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# Effect modification of the association between aerobic physical activity and diabetes-related mortality by race-ethnicity: a population-based prospective study using NHANES III and 1999-2006 NHANES

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I am submitting herewith a dissertation written by William Robert Boyer II entitled "Effect modification of the association between aerobic physical activity and diabetes-related mortality by race-ethnicity: a population-based prospective study using NHANES III and 1999-2006 NHANES." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Kinesiology and Sport Studies.

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# Effect modification of the association between aerobic physical activity and diabetes-related mortality by race-ethnicity: a population-based prospective study using NHANES III and 1999-2006 NHANES

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**Doctor of Philosophy**

**Degree**

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**William Robert Boyer II**

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## DEDICATION

To my beautiful and wonderful wife Hannah, you are my everything. Thank you for your unconditional love, encouragement and support for the past three years.

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## ABSTRACT

**Purpose:** To examine potential effect modification by race-ethnicity of the relationship between physical activity (PA) and diabetes-related mortality risk using a sample of U.S. adults from the Third National Health and Nutrition Examination Survey (NHANES III). **Methods:** The sample (n=10,717) included adults (≥20 years) who attended the Mobile Examination Center (MEC). An age-standardized PA score (PAS) was calculated from the self-reported frequency and intensity of 12 leisure-time aerobic activities. The PA scores were then grouped into three categories: inactive (PAS = 0), insufficiently active (PAS >0 - <10), and active (PAS ≥10). A PAS of 10 was chosen as a proxy cutoff for 5 bouts/wk of moderate-intensity activity, the 2007 American Heart Association/American College of Sports Medicine aerobic PA guideline. Diabetes-related mortality was defined as either death from diabetes mellitus as the primary cause or if diabetes was flagged on the death certificate as a contributing cause. Race-ethnic groups included: non-Hispanic white (NHW), non-Hispanic black (NHB), and Mexican American (MA). SAS 9.4 survey procedures were used for all statistical analyses. **Results:** There was no interaction between PA and race-ethnicity (p=0.83). Compared to inactive NHW, there was a significantly lower risk for diabetes-related mortality for insufficiently active (Hazard Ratio [HR] 0.51, 95% Confidence Interval [CI] 0.29-0.89) and active (HR 0.57, 95% CI 0.33-1.00) NHW adults. Statistical significance was not achieved for any level of activity for NHB and MA. A significant p-for-trend was revealed only for MA. **Conclusions:** The results of this study suggest that accumulation of any volume of PA is associated with a significantly lowered risk for diabetes-related mortality only in NHW. A significant dose-response relationship was only observed among MA. However, the interaction between race-ethnicity and PA did not attain statistical significance. Thus, the presence of effect modification could not be determined from

the current study, but further investigation is warranted. Given longer follow-up time in the NHANES III cohort, the ability to estimate more precise risk reductions will become plausible.

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# PART 1

# INTRODUCTION

Diabetes is a deleterious metabolic condition characterized by chronic hyperglycemia. Currently, diabetes is the seventh leading cause of mortality among adults in the United States; with the vast majority of these deaths being related specifically to type 2 diabetes (T2D) (1). Despite being a top ten cause of death, diabetes is more likely to be a contributing cause of death rather than the primary cause of death (2, 3). Furthermore, it is postulated that diabetes is underreported as a cause or contributing cause of death (2). On the death certificates of those with diabetes, approximately 35-40% have diabetes reported as a cause. Moreover, only 10-15% of people with diabetes who died have diabetes listed as the primary cause (2). Considering its strong link to cardiovascular disease (4, 5), cancers (6), kidney disease (7), and stroke (8); it is evident that diabetes plays a substantial role in mortality related to cardiovascular and metabolic causes.

Among race-ethnic groups, substantial disparities exist in the current, as well as the projected, prevalence of diabetes. American Indian/Alaskan Natives have the highest estimated prevalence of T2D (15.9%), with the next highest prevalence rates being found among Non-Hispanic Blacks (NHB, 13.2%), Hispanics (12.8%), and Asians (9.0%) (2). Those who are non-Hispanic White (NHW) have the lowest prevalence of T2D (7.6%) (2). Honeycutt et al. (9) reports the projected 50 year increase in prevalence of type 2 diabetes to be higher among NHBs (118%), Hispanics (149%) and other ethnicities (170%), as compared to NHW (104%).

The current mortality rates associated with diabetes also differ across race-ethnic groups (1). The age-adjusted death rate (per 100,000) attributable to diabetes is higher among Hispanics (25.1) and NHBs (38.2) compared to those who are NHW (18.6) (1). Moreover, compared to NHWs, NHBs and Hispanics are 2.3 and 1.5 times more likely to die from diabetes, respectively (1). It can be hypothesized that these disparities in diabetes-related mortality rates between race-

ethnic groups may be influenced, in part, by differences in physical activity (PA) participation or physiological differences through which the same levels of PA have different levels of protection (10) .

Currently, two studies have investigated the relationship between PA and diabetes-specific mortality (11, 12). Andersen et al. (11) found that participation in sports (Hazard ratio [HR] 0.34, 95% CI 0.21-0.55), cycling (HR 0.61, 95% CI 0.42-0.89), or gardening (HR 0.42, 95% CI 0.28-0.62) resulted in significantly lower HRs for diabetes-related mortality compared to those reporting no participation in these activities. In those reporting walking, statistical significance was not attained (HR 0.77. 95% CI 0.44-1.33). Williams et al. (12) examined the relationship between MET-hrs/d of walking and diabetes-related mortality. MET-hrs/d of walking were categorized into four levels: <1.07 MET-hrs/d (category 1), 1.07-1.8 MET-hrs/d (category 2), >1.8-3.5 MET-hrs/d (category 3), and ≥3.6 MET-hrs/d (category 4). Only those in category 4 (HR 0.17, 95% CI 0.04-0.73) had a significant reduction in risk for diabetes-related mortality. In a separate analysis adjusting for reported BMI, a significant HR was found for category 4 (HR 0.17, 95% CI 0.04-0.80). While these two studies provide insight into PA and diabetes-related morality, there currently exists no literature examining this relationship specifically investigating the effect modification by race-ethnicity.

The National Health and Nutrition Examination Survey (NHANES), and the available National Data Index (NDI) linked data, provides a population based opportunity to examine the extent in which PA protects against diabetes-related mortality across several race-ethnic groups. Therefore, the purpose of this study was to examine the effect modification of race-ethnicity on the association between PA and diabetes-related mortality using the NHANES III and the 1999-2006 NHANES, as well as the NDI. From the NHANES III and the 1999-2006 NHANES, self-

report PA is available to examine the association between PA and diabetes-related mortality. Also, within the 2003-2006 NHANES, objectively-measured PA, via accelerometer, is available to further investigate this relationship. Along with the data from the NDI, the multiple measures of PA will allow for a comprehensive examination of the relationship between PA and diabetes-related mortality.

**Definitions**

The following section provides details on commonly used nomenclature within the document

1. Diabetes: a deleterious metabolic condition characterized by chronic hyperglycemia (inclusive of type 1 diabetes and type 2 diabetes)
2. Type 2 Diabetes: Chronic hyperglycemia as a result of defects in insulin action and/or secretion (13).
3. Race-ethnicity:
    a. NHANES race-ethnic groups
        - *Non-Hispanic White*: Those who are white and without Hispanic origin.
        - *Non-Hispanic Black*: Those who are black and without Hispanic origin
        - *Mexican American*: Those who are of Mexican origin
        - *Other*: Those who are of Hispanic/Latino origin other than Mexican; Asians, and Native Americans as well as those who are multi-racial
    b. Other studies included in the document
        - *Hispanic:* Those of any Hispanic/Latino origin i.e. Puerto Rican, Cuban, Central/South American, Mexican (1)
4. Diabetes-related mortality: defined as either death caused by diabetes mellitus or if diabetes was flagged on the death certificate with multiple causes of death

**Statement of the problem**

Currently, no prospective population-based study has examined effect modification by race-ethnicity on the relationship between PA and diabetes-related mortality. The purpose of this study was to investigate the dose-response associations between PA and diabetes-related mortality across race-ethnic groups using data from NHANES III, the 1999-2006 NHANES, and the NDI. Below are the specific research questions to be addressed in this study.

**Research questions**

Specific to adults (20-79 years of age) participating in the NHANES III, the following research question will be addressed:

1. Is there a dose-response relationship between self-reported PA and diabetes-related mortality across race-ethnic groups?

Specific to adult participants (20-79 years of age) in the 1999-2004 NHANES the following three questions will be addressed:

2. Among the 1999-2004 NHANES, is there a dose-response relationship between self-reported PA and diabetes-related mortality across race-ethnic groups?

Questions specific to adult participants (20-79 years of age) within the 2003-2006 NHANES:

3A. Is there a dose-response relationship between accelerometer-derived minutes of MVPA and diabetes-related morality across race-ethnic groups?

3B. Is there a dose-response relationship between quartiles of accelerometer-derived total activity counts/day (TAC/d) and diabetes-related morality across race-ethnic groups?

**Significance**

This study will add to the current literature by providing insight into the race-ethnic specific associations between PA and diabetes-related morality. This will be the first study to determine the extent in which PA relates to diabetes-related morality across several race-ethnic groups.

**Delimitations**

For research question 1, the analyses will be limited to adults 20-79 years of age that did not die within the first three years of follow-up. For analyses using the 1999-2006 NHANES, the analyses will be limited to adults 40-79 years of age. Within the 2003-2006 NHANES, participants with less than four days and ≤10 hours of accelerometer wear time per day were excluded.

**Limitations**

There are several limitations inherent to the design of the NHANES. The limitations are described below.

1. The diabetes mortality variable includes death from type 1 diabetes, malnutrition-induced diabetes and other types thus the deaths from diabetes are not limited to just T2D (appendix 1, table 2)
2. Duration of PA was not measured in NHANES III, thus limiting the interpretability of total volume of activity.
3. Within the 2003-2006 NHANES, the ActiGraph 7164 model was used. A limitation with this device is limited onboard storage capacity thus devices were initialized to sample at 60-second epochs to ensure 7-days of activity could be recorded.

4. The cutpoints used within the analyses may under or overestimate time spent across intensities thus the true time spent in MVPA may not be accurately captured.
5. Self-reported PA found in both the NHANES III and 1999-2006 surveys are subject to recall bias.

# PART 2

# REVIEW OF THE LITERATURE

## Introduction

Diabetes is characterized by a chronic state of hyperglycemia resulting from defects in insulin secretion, insulin action, or both (13). It is well known that diabetes is associated with other deleterious chronic conditions such as heart disease, stroke, obesity, and kidney disease (13). The association between PA and diabetes risk and mortality within populations, including multi-ethnic populations that have diabetes, has been extensively studied. A part of understanding the epidemiological impact of diabetes relates to understanding how race-ethnicity is associated with the disease. More specifically, it is important to understand the role of race-ethnicity as an effect modifier of the relationship between PA and diabetes as well as diabetes-related mortality. However, there currently are no studies examining the effect modification of race-ethnicity on the relationship between PA and diabetes-related morality.

The following review of literature will discuss: 1. diabetes; 2. the burden of diabetes; 3. physical activity behavior and race-ethnicity; 4. physical activity and diabetes risk; 5. physical activity and mortality in those with diabetes; and 6. physical activity and diabetes-related mortality.

### Diabetes

#### *History*

The history of diabetes is both long in time as well as complex in nature. Dating back to as early as 1500 BC, there are records of individuals suffering from polydipsia and polyuria (14) which are common symptoms of chronic hyperglycemia. In early work of Greek physicians (1$^{st}$ and 2$^{nd}$ century AD), diabetes was classified by the symptoms of polydipsia and polyuria exclusively. The name diabetes was first introduced; arising from the word “diabaino” which

means “the condition that the fluid runs through” (14, 15). Further evidence of the long history of diabetes comes from the 5th century in the work of Sushruta who characterized “diabetes” by the honey-like smell and sticky consistency of one’s urine (14). However, it wasn’t until the 1800’s that the study of “diabetes” began to become a leading focus in the medical community.

Many discoveries in diabetes research were made in the 1800’s to early 1900’s (14, 15). Claude Bernard hypothesized that the excess secretion of glucose by the liver caused diabetes and he also discovered a link between glucose homeostasis and the central nervous system. Oskar Minkowski and Joseph Von Mering discovered the pancreas’ contribution to the development of diabetes. Paul Langerhans discovered the cells that secreted (what would later be known as) insulin; the islets of Langerhans.

Arguably the most important discovery in diabetes history was by Frederick Banting, John McLeod, Charles Best and James Collip, who all played roles in the discovery that the defect in secretion or lack of insulin caused diabetes to develop. It is important to note that Frederick Banting and James McLeod are credited with the discovery of insulin (as the Nobel Prize was awarded to them both), however both Best and Collip served as co-investigators in the process (14, 15). It was from this work that treatment of diabetes flourished beginning in the mid 1950’s.

It was not until 1949, in an article authored by Himsworth (16), that the notion of different “types” of diabetes were discussed. Himsworth concluded that “abnormal hyperglycemia” was either a result of impaired carbohydrate metabolism (i.e. insulin secretion defects) or an inability to store carbohydrates. Further suggestion of two types was discussed by Yalow and Berson in 1960 (17), who noted that despite still making their own insulin, some study participants still had diabetes; suggesting that “insulin sensitivity” could be a cause of

diabetes and not just defects in insulin secretion. It was not until 1979 that the diabetes classification system was introduced to include the four types: insulin-dependent/type 1, non-insulin-dependent/type 2, gestational, and environmental (18).

*Type 2 diabetes*

Type 2 diabetes (T2D) was formally known as non-insulin dependent diabetes mellitus until 1997 (18). It is characterized by defects in insulin action and is primarily driven by increasing resistance to insulin resulting in chronic hyperglycemia (13). Moreover, T2D makes up 90-95% of all cases of diabetes (13). Until 1997, T2D was diagnosed using one of two methods; a fasting plasma glucose (FPG) ≥140 mg/dL or a 2-hr plasma glucose ≥200 mg/dL following a 75-g oral glucose tolerance test (OGTT) (13). Beginning in 1997, the diagnostic criteria for T2D changed in regards to FPG; from ≥140 mg/dL to ≥126 mg/dL (13).

In 2009, the American Diabetes Association began recommending the use of glycosylated hemoglobin (A1c) to diagnose T2D, using a cutpoint of ≥6.5% (13). The justification for this recommendation is rooted in A1c having greater pre-analytical stability compared to FPG, no need for fasting to measure, better reflection of chronic glycemic status over the course of two to three months, and it is less affected by stress and illness (13). Furthermore, the International Expert Committee on Diabetes has highlighted the vast epidemiological evidence in support of the use of A1c to diagnose diabetes (13, 19). Improvements in A1c as a diagnostic tool have been recently highlighted as the assays are now standardized (13). It is important to note that both FPG and 2-hr OGTT are still validated methods to diagnose T2D.

Several criticisms have been raised in regards to using A1c as a diagnostic tool (20-22). Kilpatrick et al. (22) raised the point that A1c is higher in older adults compared to younger

adults despite similar glucose tolerance. Furthermore, there may be inherent differences across race-ethnic groups that could influence or potentially mis-represent true estimates of diabetes prevalence specific to race-ethnicity (21-23). Guo and colleagues (21) found differences in the relationship between A1c, FPG and 2-hr OGTT in a sample from the 2005-2010 NHANES. Results indicated discrepancies in FPG and A1c, as at a given A1c value, non-Hispanic blacks (NHB) had lower FPG and 2-hr OGTT values. In contrast, at given FPG or 2-hr OGTT, NHB had higher A1c values.

In a recent study conducted by Lacy and colleagues (23), A1c, FPG, and 2-hr OGTT values were compared in a sample of African Americans (AAs) with and without sickle cell trait (SCT). The results of the analysis indicated that A1C was significantly lower in those with SCT at a given FPG and 2-hr OGTT. Given that the prevalence of SCT is approximately 8-10% in AAs (24), it is possible that diabetes estimates in AAs are underestimated in population based studies when using A1c.

**The burden of diabetes**

*Prevalence*

It is well known that the burden of diabetes (inclusive of type 1 and T2D) has increased since the late 1950's quantified by increasing prevalence across years. Moreover, these prevalence estimates have consistently been higher among minority groups compared to non-Hispanic white (NHW). It is also projected that the disparities in diabetes prevalence estimates will continue to expand in the next 30+ years; which is a major public health concern. Along with the current and projected diabetes disparities, the diabetes-specific mortality rates differ across race-ethnic groups.

Diabetes has increased in a linear fashion beginning in 1958 (0.93%) to the late 1990s (1998: 3.8%) (25). Since the late 1990's, the prevalence of diabetes has increased drastically. According the Centers of Disease Control and Prevention (CDC), using self-report data from the National Health Interview Survey (NHIS), the current national diabetes prevalence rates among adults is 9.3% (2, 25). It is important to note that the surveillance system used to track diabetes, as well as the definition (self-report vs measured values), influence prevalence estimates. For example, a study using the 2011-2012 NHANES (26), diabetes prevalence was 14.3% based on self-report diabetes, and measured A1c ≥6.5%, FPG ≥126 mg/dl, or 2-hr OGTT ≥200 mg/dl.

Disparities in the prevalence of diabetes exist across race-ethnic groups. Based upon self-reported data from the 2010-2012 NHIS and 2012 Indian Health Service's National Patient Information Reporting System (2), the current national prevalence estimates of diagnosed diabetes is higher among Asians (9.0%), Hispanics (12.8%), non-Hispanic blacks (NHBs) (13.2%), and American Indians/Alaskan Natives (15.9%) compared to NHWs (7.6%). These disparities in diabetes prevalence across race-ethnicity have been observed since the 1970's. Using data from NHANES I (1971-1975), II (1976-1980), III (1988-1994) and 1999-2004, Zhang et al. (27) examined the prevalence of self-reported diabetes among NHW, NHB, and Mexican Americans (MA) (Table 2.1). This study found that the prevalence of diabetes increased across all race-ethnic groups over the course of the NHANES cycles.

Table 2.1. Prevalence of self-reported diabetes across cycles of the NHANES

| | NHANES 1 1971-1975 | NHANES II 1976-1980 | NHANES III 1988-1994 | NHANES 1999-2004 |
|---|---|---|---|---|
| **NHW** | 2.9% | 4.4% | 5.9% | 7.8% |
| **NHB** | 4.5% | 9.0% | 10.6% | 13.8% |
| **MA** | 3.4% | 7.2% | 12.6% | 13.2% |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American; NHANES: National Health and Nutrition Examination Survey

Source: Zhang Q, Wang Y, Huang ES. Changes in racial/ethnic disparities in the prevalence of Type 2 diabetes by obesity level among US adults. Ethn Health. 2009;14:439-457.

The current race-ethnic specific prevalence rates of diabetes differ dependent upon the definition used to denote diabetes. For example, Menke et al. (26) investigated the prevalence of total diabetes (diagnosed and undiagnosed) across race-ethnic groups using data from the 2011-2012 NHANES. Total diabetes was defined as either: self-reported physician diagnosis, measured A1c ≥6.5%, FPG ≥126 mg/dL, or 2-hr OGTT ≥200 mg/dL. Those classified as NHB (21.8%) Asian (20.6%) or MA (23.8%) had significantly higher prevalence rates for total diabetes compared to NHW (11.3%). Moreover, these rates are all significantly higher than the aforementioned prevalence rates from the NHIS (2, 25).

The prevalence of diabetes is projected to vastly increase by the year 2050. Overall, in the U.S., the projected prevalence will increase to between 21% and 33% by the 2050 (28). Two studies have provided projected prevalence increases stratified by race-ethnicity (9, 29). Using data from the 1994-2000 NHIS, Honeycutt et al. (9) projected the 2050 prevalence rates of diabetes will be higher among NHBs (118%), Hispanics (149%) and other ethnicities (170%), compared to NHW (104%). A similar analysis and model by Narayan et al. (29), using the 1984-

2004 NHIS, found similar 2050 projected prevalence rates; NHBs (107%), Hispanics (127%) and other ethnicities (158%), NHW (99%).

*Diabetes mortality and race-ethnicity*

Race-ethnic disparities in diabetes-related mortality rates have been confirmed across multiple population-based surveys (1, 2, 30, 31). Historically, the percentage of mortality related to diabetes has been higher among ethnic minorities compared to NHW. Using data from the NHIS, the rates of mortality from diabetes was estimated between NHW and NHB males and females from 1980-2009 (31). While the incidence of death from diabetes declined across all groups, there was a distinct pattern in which mortality rates were higher in NHBs compared to NHWs. Furthermore, the rates were much higher across the years in NHB males compare to NHW males and females as well as NHB females (appendix 3). In a study by Beydoun et al. (30), utilizing data from the NHANES III (1988-1994), the mortality rate attributable to diabetes was significantly lower in NHWs compared to NHBs (NHW:8.4% vs NHB:10.8%, $p<0.001$), as well as in NHWs when compared to MAs (NHW:8.4% vs MA:13.9%, $p=0.002$). According to the 2014 final deaths report, the estimate of deaths attributable to diabetes (per 100,000) is higher among Hispanics (25.1) and NHBs (38.2) compared to NHW (18.6) (1). When compared to NHWs, NHBs and Hispanics are 2.3 and 1.5 times more likely to die from diabetes, respectively (1).

A recent analysis by Stokes et al. (32) examined the population-attributable fraction (PAF) of mortality related to diabetes, as well as the prevalence of diabetes-related mortality. Data from the NHIS (1997-2009) and NHANES (1999-2010) were used for this study. A total of 282,322 participants aged 30-84 were used in the sample. The PAF for mortality from diabetes was 11.1% in NHW, 13.0% in NHB, and 13.0% in Hispanics. The prevalence of diabetes being

reported as the underlying cause was 2.6% in NHW, 5.0% in NHB, and 7.0% in Hispanics. The prevalence of diabetes being assigned as a contributing cause of death was 9.7% in NHW, 14.4% in NHB, and 15.7% in Hispanics. From these results it is evident that diabetes-related mortality affects those who are NHB and Hispanic more than those who are NHW.

## Physical activity behavior and race-ethnicity

### *Physical activity (PA) behavior*

PA is associated with a plethora of positive health outcomes and lower risk for T2D. In order to understand the population-level impact of PA on T2D, it is imperative to know the PA behavior of adults. Beyond this, it is important to know PA behavior across race-ethnic groups as this may explain disparities in different health outcomes. The following section will detail the prevalence of PA participation in the U.S.; comparing different survey methods, self-report vs. accelerometry-derived PA, and the differences in these across race-ethnicity.

Several survey systems, such as the NHIS, BRFSS and NHANES, examine the prevalence of meeting the 2008 Department of Health and Human Services (DHHS) aerobic physical activity guideline (PAG) to understand the PA behaviors in U.S. adults. Quantified, the aerobic PAG is either ≥150 min/wk of moderate-intensity PA or ≥75 min/wk of vigorous-intensity PA (33). Furthermore, it is important to note that PA attributable to meeting these guidelines can come from all domains including: LTPA, transportational PA, occupational PA and domestic PA.

Using self-report data from the 2015 NHIS, the current national prevalence of adults meeting the 2008, through leisure-time PA (LTPA), is approximately 49% (34). However, depending upon the self-report survey, the current estimates of PA behavior vary in U.S. adults (35, 36). Using data from the 2013 Behavioral Risk Factor Surveillance System (BRFSS), the

national estimate for meeting the 2008 PAG (LTPA) was 50.2% in 2015 (37). In an analysis by Keadle et al. (38), using self-report data from three different population surveys, (2011-2012 NHANES, 2013 NHIS, and 2013 BRFSS), the prevalence of older adults (≥65 years) meeting the 2008 DHHS aerobic PAG (using only LTPA) differed across surveys; 35.8% for NHIS, 27.3% for NHANES, and 44.3% for BRFSS.

When examining PA participation including other domains (i.e. transportational and household), the prevalence estimates of PA increase. It is important to note that both the NHIS and BRFSS only assess LTPA. In a 2011 analysis using self-report data from the 2005-2006 NHANES, Tucker et al. (39) compared the prevalence of meeting the 2008 DHHS PAG by summarizing PA participation across several domains of self-report PA (LTPA, transportation and household). The PAG were categorized in three ways: 150 minutes of moderate to vigorous PA (MVPAG), the second way was calculated by weighing each minute of vigorous activity as two minutes of moderate PA (MV2PAG), or 500 MET-min/wk (METPAG). For all three categories of PAG, three levels were denoted: none (no PA), insufficient (from 1 to <150 min or 500 MET-min/wk), and meeting the PAG (≥150 min or ≥500 MET-min/wk). The prevalence of meeting the PAG was 59.6% (MVPAG), 62.0% (MV2PAG), and 65.7% (METPAG).

Differences in the estimation of PA behavior in population-based surveys exist when measuring PA with objective methodologies such as accelerometers (40-42). Furthermore, within accelerometer research, the use of different cut-points can impact the estimates of time spent in MVPA (40, 41, 43) further impacting the prevalence of meeting the PAG. In a study using the accelerometry data form the 2003-2006 NHANES, Boyer et al. (40) found significant differences in the mean bouted minutes of MVPA comparing the 2020 cpm (7.0 ± 0.4 minutes) to the 760 cpm (15.2 ± 0.1 minutes) cutpoint. In an analysis by Watson et al. (43) using data from the 2003-

2006 NHANES, investigators compared the prevalence of meeting the 2008 DHHS aerobic PAG using 12 different accelerometer cut-points commonly used to denote MVPA and estimates ranged from 6.3-98.3%.

As highlighted by the aforementioned studies as well as Price et al. (36), the methodology employed to measure PA will drastically affect prevalence estimates of PA behavior due to inherent limitations specific to the methodologies. Within the self-report data the prevalence of meeting the aerobic PAG ranges from 49.0% (35) to 65.7% (39). For accelerometry-derived PA, the prevalence ranges from 6.3% to 98.3% (43).

*Physical activity behavior and race-ethnicity*

As mentioned previously, there are distinct disparities in the prevalence of diabetes across race-ethnic groups (2, 26, 27). Furthermore, it is equally important to note that these disparities are projected to increase through the year 2050 (9, 28, 29). To begin to understand how PA relates to T2D risk between different race-ethnic groups, it is important to grasp the population-level prevalence of PA behavior in these groups. As with national estimates, there are differences in PA behavior when examining PA by self-report vs. accelerometry methods. However, despite these differences specific to measurement method, PA participation tends to be lower in NHBs compared to other race-ethnic groups.

According to the estimates from the CDC using data from the 2015 NHIS, the prevalence of meeting the 2008 DHHS aerobic PAG differs across race-ethnicity; 42.4% (NHB), 43.0% (Hispanics), and 52.9% (NHW). Keadle et al. (38), examined the prevalence of meeting the 2008 DHS aerobic PAG among older adults (≥65 years), stratified by race-ethnicity. This population-level study used data from the 2011-2012 NHANES, the 2013 NHIS, and the 2013 BRFSSS.

Across the three surveys, the prevalence of meeting the PAG (via LTPA) was significantly lower in those who were Hispanic or NHB, compared to NHW (Table 2.2).

Table 2.2. Prevalence of meeting the 2008 DHHS aerobic PAG via self-reported LTPA in older adults (≥65 years): stratified by race-ethnicity

| | NHIS | BRFSS | NHANES |
|---|---|---|---|
| **NHW** | 37.2% | 46.4% | 30.1% |
| **NHB** | 27.5% | 33.5% | 16.3% |
| **Hispanic** | 29.6% | 33.5% | 14.6% |

NHW: non-Hispanic white; NHB: non-Hispanic black;; NHANES: National Health and Nutrition Examination Survey; NHIS: National Health Interview Survey; BRFSS: Behavioral Risk Factor Surveillance System

Source: Keadle SK, McKinnon R, Graubard BI, Troiano RP. Prevalence and trends in physical activity among older adults in the United States: A comparison across three national surveys. Preventive Medicine. 2016;89:37-43.

In the aforementioned analysis by Tucker et al. (39), using self-reported data from the 2005-2006 NHANES, investigators stratified their analysis further across race-ethnicity (NHW, NHB and MA). Results revealed that meeting the prevalence of meeting the PAG (LTPA, transportational and household) was significantly lower in those who were MA or NHB compared to NHW (Table 2.3).

Table 2.3. Prevalence of meeting the 2008 DHHS aerobic PAG via self-reported PA (LTPA, transportational PA and household PA) stratified by race-ethnicity: 2005-2006 NHANES

| | MVPAG | MV2PAG | METPAG |
|---|---|---|---|
| **NHW** | 63.0% | 65.0% | 68.8% |
| **NHB** | 47.7% | 52.1% | 55.1% |
| **MA** | 40.7% | 43.7% | 48.4% |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American; NHANES: National Health and Nutrition Examination Survey; MVPAG: 150 minutes of moderate to vigorous PA; MV2PAG: weighing each minute of vigorous activity as two minutes of moderate PA; METPAG: 500 MET-min/wk.

Source: Tucker JM, Welk GJ, Beyler NK. Physical activity in U.S.: adults compliance with the Physical Activity Guidelines for Americans. Am J Prev Med. 2011;40:454-461.

In contrast to the self-report estimates, accelerometry estimates yield different results, both in prevalence as well as race-ethnic differences. For accelerometry-derived PA using the 2003-2006 NHANES, Tucker et al. (39) showed that those who were categorized as MA had higher prevalence rates for meeting the 2008 DHHS PAG. When examining PA categorized as MVPAG (150 minutes of moderate to vigorous PA) the prevalence was 8.2% (NHW), 7.7% (NHB) and 9.1% in MA. For the MV2PAG (weighing each minute of vigorous activity as two minutes of moderate PA) the prevalence was 10.1% (NHW), 8.0% (NHB) and 9.9% in MA. For the METPAG (500 MET-min/wk) the prevalence was 46.1% (NHW), 37.6% (NHB) and 46.8% in MA.

Watson et al. (43) further stratified their analysis by race-ethnicity and reported the median prevalence of meeting the 2008 DHHS PAG measured via accelerometer. Several cut-points denoting MVPA were used based on either studies examining walking and running (WR) or those using lifestyle activities. While not statistically different, there were differences in the

prevalence of meeting the PAG across race-ethnicity depending upon the cut-point used (WR: NHW: 12.0%, NHB: 9.9%, MA: 12.9%, other: 11.8%), (Lifestyle: NHW: 76.6%, NHB: 75.1%, MA: 84.6%, other: 77.8%). Similar to the results found by Tucker et al. (39), NHB had lower prevalence of meeting the PAG.

To summarize, there are distinct differences between race-ethnic groups when examining PA behavior specifically when using self-report methodologies to measure PA. Consistently, NHW have been shown to report higher prevalence of meeting the 2008 DHHS aerobic PAG compared to other race-ethnic groups. In contrast to self-report estimates, accelerometry-derived PA consistently showed higher estimates in MA. However, similar to self-report, NHB consistently have lower participation in PA.

**Physical activity and diabetes risk**

There is a well-researched and defined inverse association between PA and T2D risk (44, 45). Two recent meta-analyses (44, 45) have provided a thorough and detailed examination of this association across over 100 different prospective cohort studies. From these two studies evidence of significant reductions in risk for T2D are associated with total PA (44, 45), LTPA (44, 45), vigorous PA (44), moderate PA (44), light PA (44), walking (44), resistance training (44), and occupational PA (OPA) (44). Furthermore, a clear, non-linear dose-response was found in a meta-analysis by Smith et al. (45), indicating that a doubling in PA volume does not necessarily equate to a double in risk reduction. However, it is evident that more PA is associated with a more pronounced reduction in risk. This section will detail the results of these meta-analyses.

In 2015, Aune et al. (44) systematically reviewed and conducted a meta-analysis across 81 prospective cohort studies examining the relationship between PA and T2D risk. Domains of

PA examined included: total PA, LTPA, vigorous PA, moderate PA, light PA, walking, resistance training, and OPA (Table 2.4).

Table 2.4. Domains of PA and T2D risk: Results of Aune et al. (34) comparing the most vs least active.

| PA Domain | RR for T2D (RR, 95% CI) |
|---|---|
| **Total PA** | 0.65 (0.59-0.71) |
| **LTPA** | 0.74 (0.70-0.79) |
| **Vigorous PA** | 0.61 (0.51-0.74) |
| **Moderate PA** | 0.68 (0.52-0.90) |
| **Light PA** | 0.66 (0.47-0.79) |
| **Walking** | 0.85 (0.79-0.91) |
| **Resistance training** | 0.72 (0.58-0.84) |
| **Occupational PA** | 0.85 (0.79-0.92) |

PA: Physical Activity; RR: Relative Risk; CI: Confidence Interval

Source: Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis. European Journal of Epidemiology. 2015;30:529-542.

In order to examine the potential dose-response relationship between PA and T2D, Aune et al. (44) conducted additional analyses for studies reporting LTPA. For the dose-response analyses, PA was categorized in three ways: Every 20 MET-hrs/wk, every 5 MET-hr/wk, and every 1000 kcals/wk. For every 20 MET-hrs/wk of LTPA, there was a significant summary reduction in the risk for T2D (RR 0.85, 95% CI 0.81-0.89). For every 5 hrs/wk of LTPA, there was a significant summary reduction in risk for T2D (RR 0.75, 95% CI 0.67-0.85). For every

1000 kcals/wk, a significant summary reduction in risk for T2D (RR 0.87, 95% CI 0.79-0.95) was found.

In the same study, separate dose-response analyses were conducted for vigorous PA, light PA, resistance training and walking. For vigorous PA, light PA, and resistance training, PA was examined in increments of 5 hrs/wk. For walking, three PA methods were used: every 5 hrs/wk, every 2 hrs/wk, and every 10 MET-hrs/wk. Specific to vigorous PA, for every 5 hrs/wk a significant summary reduction is risk for T2D was found (RR 0.69, 95% CI 0.58-0.82). For light PA, a significant summary reduction is risk for T2D was revealed per every 5 hrs/wk (RR 0.60, 95% CI 0.44-0.82). For every 10-MET hrs/wk of walking, no significant relationship was found (RR 0.95, 95% CI 0.88-1.02). For every 2 hrs/wk of walking, a significant association was found (RR 0.92, 95% CI 0.85-0.99). In studies examining resistance training, every 5 hrs/wk of resistance training was associated with a significantly lower risk of T2D (RR 0.70, 95% CI 0.58-0.84).

In a 2016 meta-analysis, Smith et al. (45) expanded on the results from Aune et al. (44) by conducting a more harmonized dose-response analysis examining PA and T2D. A total of 28 cohort studies were included in the meta-analysis. Significant summary effects for every 10 MET-hrs/wk accumulated of total PA (RR 0.95, 95% CI 0.93-0.98) and LTPA (RR 0.83, 95% CI 0.79-0.87). In a separate analysis, a non-linear dose-response was investigated by examining PA in relation to the 2008 aerobic PA guidelines (11.25 MET-h/wk) and volumes equating to double that of the 2008 PA guidelines (22.5 MET-hr/wk). Significant summary effects were found for 11.25 MET-hr/wk (RR 0.74, 95% CI 0.69-0.80) and 22.5 MET-hr/wk (RR 0.64, 95% CI 0.54-0.73). At volumes of 60 MET-hr/wk, a significant summary effect was found (RR 0.47, no CI reported).

It is evident from both of the aforementioned meta-analyses (44, 45) that a clear inverse relationship exists between PA and T2D. More specifically, Aune et al. (44) showed that total PA, LTPA, vigorous PA, moderate PA, light PA, walking, resistance training, and OPA are all associated with reductions in the risk of T2D. Furthermore, there is a significant dose-response relationship between vigorous PA, light PA, hrs/wk of walking and hrs/wk of resistance training. No relationship was found between MET-hrs/wk of walking and T2D risk. Smith et al. (45) further added to this relationship, specifically for total PA and LTPA, by showing a non-linear dose-response between MET-hrs/wk and T2D risk.

**Physical activity and the risk of type 2 diabetes: the effect modification by race-ethnicity**

A recent meta-analysis by Boyer et al. (10) (appendix 2) examined how race-ethnicity modifies the established association between PA and T2D. Both PubMed and Embase databases were systematically searched up to June 2016. Studies met the following inclusion criteria: human participants who were without T2D at the start of the studies and were adults (≥18 years) at the time of follow-up; assessed aerobic-based PA; published or available in English; were prospective cohort studies; assessed and reported the race-ethnicity specific relative risks (RR) for T2D; adjusted risk estimates for age; and allowed for the determination of a most versus least physically active group. The race-ethnic groups included were as follows: NHW, NHB, Asian, Hispanic and American Indian. Individual study RRs (n=27) were extracted and analyzed to assess the relationship between PA and T2D that compared the most to the least active group across the chosen race-ethnic groups. Moreover, the effect modification of race-ethnicity was analyzed in those meeting the current 2008 DHHS moderate-intensity PA recommendations compared to those not meeting the recommendations.

A statistically significant summary effect was found for NHWs (RR 0.71, 95% CI 0.60-

0.85), Asians (RR 0.76, 95% CI 0.67-0.85), Hispanics (RR 0.75, 95% CI 0.64-0.89), and American Indians (RR 0.73, 95% CI 0.60-0.88). The summary effect for NHB (RR 0.91, 95% CI 0.76-1.08) was non-significant. For analyses examining the 2008 aerobic PAG, there was a trend towards significance for NHWs (RR 0.75. 95% CI 0.55-1.01, p=0.06) and Asians (RR 0.80, 95% CI 0.64-1.01, p=0.06), but the estimates did not attain statistical significance. The results for NHBs (RR 1.26, 95% CI 0.84-1.90) and Hispanics (RR 0.95, 95% CI 0.66-1.65) did not attain statistical significance.

Several physiological mechanisms have been proposed that could explain the lack of significance found for NHBs in this study. In short, these include: 1) genetic predisposition, 2) compromised hepatic suppression of endogenous glucose production in response to insulin, 3) lower insulin sensitivity in the peripheral tissues (specifically skeletal muscle) despite similar volumes of aerobic PA, 4) a down regulation of insulin receptors driven by hyperinsulinemia and decreased hepatic insulin clearance, 5) increases in intramuscular adipose tissue and intra-myocellular lipid content deposits, and 6) skeletal muscle fiber type differences. Appendix 2 greatly expands on these mechanisms.

*Summary of the effect modification of race-ethnicity on PA and T2D risk*

The recent meta-analysis by Boyer et al. (10)(appendix 2) provided detailed and much needed insight into the effect modification of race-ethnicity on the established relationship between PA and T2D. The results indicate that those who identify as NHW, Asian, American Indian, or Hispanic had similar risk reductions ranging from 24% to 29%. Furthermore, those who identified as NHB had no significant reduction in risk. The results of this study can be postulated to also be reflective of how race-ethnicity modifies the relationship between PA and mortality; more specifically diabetes-related mortality. However, research is needed.

**Physical activity and mortality in those with diabetes**

From a public health perspective, it is equally important to understand how PA, T2D and mortality are associated, as the results from Boyer et al (appendix 2) indicate that protection from T2D is not equally shared across other race-ethnic groups. Considering the strong association between T2D and mortality (46-48), it is necessary to examine if an effect modification by race-ethnicity exists when considering mortality. To further understand the impacts of PA and T2D, the next section will provide a comprehensive examination of the literature investigating: a) the relationship between PA and mortality in those with diagnosed T2D, b) the effect modification of this relationship by race-ethnicity, and c) the relationship between PA and diabetes-related mortality.

**Physical activity, all-cause and cardiovascular (CVD) mortality in those with diabetes**

For this review, a total of 13 studies (49-61) were identified that examined the relationship between physical activity and mortality (all-cause and CVD) specifically among those with T2D. To understand this relationship, PA has been examined using total PA (PA across multiple domains) as well as individual domains (occupational, transportational, and LTPA) and walking. Among these 13 studies, seven examined total PA (50, 52-54, 56, 57, 60), seven examined LTPA (49, 51, 55-57, 59, 61), one examined occupational PA (51), one examined transportational PA (51), one examined domestic PA (56), and five examined walking (50, 56-59). The following section will discuss the relationship between PA and all-cause or CVD mortality in participants with diabetes; organized by domain. A summary and meta-analysis is presented at the end of this section to provide insight into the overall relationship between PA and mortality in those with diabetes.

*Total PA*

All seven studies examining total PA and mortality among those with T2D examined all-cause mortality (50, 52-54, 56, 57, 60) and four examined CVD mortality (50, 52, 56, 57). Gregg et al. (50) investigated the relationship between total PA and mortality in 2,896 adults with T2D who participated in the 1990-1991 NHIS. Three categories were created for total PA (low: 0 hr/wk, moderate: 0-1.9 hr/wk, and high: ≥2 hr/wk). Following adjustment for age, gender, race, body mass index, self-rated health, smoking, weight loss approaches, hospitalizations, hypertension and use of antihypertensive medications, physician visits, limitations caused by CVD and cancer, and level functional limitation, significantly lower risk for all-cause mortality was revealed in those who were categorized as high total PA (HR 0.71, 95% CI 0.59-0.87). No association was found for total PA and CVD mortality.

In another study by Hu and colleagues (52), using 3,708 Finnish adults with T2D, the relationship between PA (LTPA and occupational) and mortality was examined. Physical activity was defined as low (light levels of occupational, commuting (<1 min), and leisure-time PA), moderate (reported only one of the all three types of moderate to high PA) or high (reported two or three types of moderate to high PA). Following adjustment for age, gender, study year, education, BMI, systolic blood pressure, total cholesterol level, and smoking, significantly lower risks for all-cause mortality was found in those reporting PA in the moderate (HR 0.61, 95% CI 0.51-0.73) or high (HR 0.55, 95% CI 0.47-0.66) categories. Similar results were found for CVD mortality.

Jonker et al. (53) examined the risk of all-cause mortality in 5,209 participants from the Framingham Heart study with T2D. Physical activity was assessed via self-reported time spent in light, moderate or vigorous activities over a week. Time spent (hrs/wk) were then multiplied

by the metabolic cost of activity (i.e. 0.25 l/min for sleep) and then weighted according to intensity (1.1: sedentary, 1.5: light PA, 2.4: moderate PA, and 5: vigorous PA). The weighted hours were then converted into tertiles to examine a dose-response relationship. Significantly lower risk for all-cause mortality was found for those in tertile 3 (HR 0.53, 95% CI 0.39-0.72) compared to tertile 1.

In 712 adults with T2D, Loprinzi (54) examined the relationship between objectively-measured PA and the risk of all-cause mortality within the 2003-2006 NHANES. Activity was categorized as minutes spent above 100 counts per minute (cpm). After adjustment for age, gender, race-ethnicity, serum cotinine, poverty-to-income ratio (continuous); C-reactive protein (CRP), cholesterol medication use, blood pressure medication use, diabetes medication, glycosylated hemoglobin A1C and other illness, a significantly lower risk for mortality was found (HR 0.68, 95% CI 0.56-0.83) for every 60 min of accrued activity above 100 cpm.

Sadarangani et al. (56) examined the dose-response relationship between PA and all-cause mortality and CVD mortality in a sample with T2D. PA was categorized into three levels: none (no reported activity), some (0.1–7.4 MET-hr/wk) and meeting the recommendations (≥7.5 MET-hr/wk). Those reporting some activity had significantly lower risk for both all-cause (HR 0.74, 95% CI 0.61-0.89) and CVD mortality (HR 0.68, 95% CI 0.51-0.92). Those reporting meeting the recommendations had significantly lower risk for both all-cause (HR 0.65, 95% CI 0.53-0.79) and CVD mortality (HR 0.60, 95% CI 0.44-0.82) compared to those reporting none.

Using data from the European Prospective Investigation into Cancer and Nutrition study (EPIC) study, Sluik et al. (57) investigated the relationship between LTPA and all-cause mortality in participants with T2D. Participants reported the time spent in activity and quartiles (inactive, moderately inactive, moderately active, and active) were created based off of the sum

MET-hr/wk for total PA. Those who were categorized as moderately inactive (HR 0.68, 95% CI 0.54-0.76) and moderately active (HR 0.58, 95% CI 0.43-0.77) had significantly lower risk for all-cause mortality. Moderately inactive (HR 0.46, 95% CI 0.28-0.74), moderately active (HR 0.31, 95% CI 0.15-0.60), and active participants (HR 0.48, 95% CI 0.25-0.94) all had lower risk for CVD mortality compared to inactive participants.

Using data from 1,013 participants with T2D in the Greek EPIC study, Trichopoulou et al. (60) examined the relationship between total PA and the risk of all-cause mortality. Activity was categorized into quintiles (1: <30, 2: 30 to <32, 3: 32 to <34, 4: 34 to <37, 5: ≥37) of MET-hrs/d based on self-reported PA. A summary dose-response analysis was conducted per 1 unit increase in quintile. A significant dose-response relationship was found for every 1-unit increase in quintile and all-cause mortality (HR 0.76, 95% CI 0.63-0.92).

*Leisure-time PA*

Seven studies examined LTPA and all-cause mortality risk (49, 51, 55-57, 59, 61) and four examined LTPA and CVD mortality (49, 51, 57, 59) in participants with T2D. Using data from the NHANES I, Ford et al. (39) examined the risk for all-cause and CVD mortality among 602 participants with T2D. Leisure-time PA was categorized from a single question: "Do you get much exercise in things you do for recreation?". Three categories were used: much exercise, moderate exercise, or little to no exercise. There were no significant reductions in risk for all-cause mortality or CVD mortality across LTPA categories.

In a 2004 study conducted by Hu et al. (51) the relationship between LTPA and the risk of all-cause and CVD mortality was examined among 3,316 Finnish adults with T2D. LTPA was categorized into three levels: 1) low (almost completely inactive), 2) moderate (some physical activity for ≥4 h/wk) and 3) high ((vigorous physical activity for ≥3 h/wk) Following adjustment

for age, gender, study year, body mass index, systolic blood pressure, cholesterol, smoking, and other types of PA, significantly lower risks for all-cause mortality were found for moderate (HR 0.86, 95% CI 0.75-0.98) and high (RR 0.72, 95% CI 0.55-0.95) LTPA. For CVD mortality, those categorized as moderate (HR 0.84, 95% CI 0.71-0.99) or high (HR 0.69, 95% CI 0.49-0.99) LTPA had significantly lower risk.

Using data from NHANES III, Nelson and colleagues (55) investigated the association between LTPA and all-cause mortality in 1,507 adults with T2D. PA was assessed via self-reported time spent across several activities which was then converted to MET-min/wk based on intensity specific levels. Leisure-time PA was dichotomized: those reporting none or those reporting any LTPA. In participants reporting any LTPA participation, a significantly lower risk for all-cause mortality was found (HR 0.63, 95% CI 0.49-0.80).

Sadarangani et al. (56) investigated the relationship between LTPA (sport and exercise participation) and all-cause and CVD mortality in a sample with T2D. Participants reported frequency, duration and type of activity; with at least 15 min per bout of activity. Intensity was examined by asking if the participants were out of breath, or sweaty when performing the activity. Activity was categorized in three levels based on the calculated MET-minutes for reported activities: none, below median, or above median. Significant reductions in risk for all-cause mortality were found for those in the median (HR 0.74, 95% CI 0.55-0.99) and above median (HR 0.71, 0.51-0.99) groups compared to those with no reported activity. No significant associations were found for LTPA and CVD mortality.

Using data from the EPIC study, Sluik et al. (57) investigated the relationship between PA and all-cause mortality in participants with T2D. Participants reported time spent in activity and quartiles (inactive, moderately inactive, moderately active, and active) were created based

off of the sum MET-hr/wk for LTPA. Following adjustment for covariates, moderately inactive (HR 0.77, 95% CI 0.60-0.99) and active (HR 0.62, 95% CI 0.46-0.85) participants had lower risk for all-cause mortality. Only active participants had lower risk for CVD mortality (HR 0.30, 95% CI 0.14-0.64).

Tanasescu et al. (59) examined the association between PA and all-cause mortality in a sample of 3,058 men with T2D from the Health Professionals' follow-up study. Quintiles of PA were created based on MET-hr/wk calculated from self-reported participation in LTPA. Significantly lower risk for all-cause mortality was found in those categorized into the third (HR 0.64, 95% CI 0.45-0.91), fourth (HR 0.64, 95% CI 0.45-0.90) and fifth (HR 0.65, 95% CI 0.45-0.93) quintiles. It is evident that a threshold effect was found with no significant decreases in mortality risk existing past the third quintile. No significant relationship was found for CVD mortality.

In an analysis using data from the Aerobics Center Longitudinal Study (ACLS), Wei et al. (61) examined the relationship between LTPA and all-cause mortality in participants with T2D. Activity was defined as reporting any participation in walking, jogging, or aerobic exercise in their leisure-time in the 3 months before examination. Following adjustment for age, examination year, smoking, alcohol, baseline CVD, family CVD, high cholesterol, diabetes status, glucose, blood pressure, and overweight status, those who reported any activity had significantly lower risk for all-cause mortality (HR 0.56, 95% CI 0.40-0.78) compared to inactive participants.

*Occupational PA, transportational PA, and domestic PA*

In the single study examining occupational PA, Hu et al. (51) examined the relationship between PA and the risk of all-cause and CVD mortality in 3,316 Finnish adults with T2D.

Occupational PA was categorized as light (physically very easy, sitting office work), moderate (standing and walking) or active (walking and heavy lifting). Following adjustment for age, gender, study year, BMI, systolic blood pressure, cholesterol, smoking, and the two other types of PA (transportational and LTPA), significantly lower risks for all-cause mortality (HR 0.67, 95% CI 0.57-0.78) and CVD mortality (HR 0.69, 95% CI 0.57-0.85) were found, only in the active group compared to the light group.

The single study examining transportational PA and the risk for all-cause and CVD mortality was also conducted by Hu et al. (51) using the same participants as the previously mentioned study. Transportational PA was categorized into three levels: 1) motorized transportation or no work (0 minutes of walking or cycling), 2) walking or bicycling 1 to 29 minutes, and 3) walking or bicycling for ≥30 minutes. In the full-adjusted models, no significant reduction in mortality risk was found for any volume of transportational PA.

In an analysis of 3,038 participants with T2D from the Scottish Health Survey and Health Survey for England, Sadarangani et al. (56) examined the dose-response relationship between domestic PA and all-cause mortality and CVD mortality. Participants reported time spent in household or housework activities for at least 30 minutes. PA was categorized into three gender-specific levels: none (no reported activity), below median and above median PA. For all-cause mortality, those categorized as being below median MET-hr/wk had a significant reduction in all-cause mortality risk (HR 0.77, 95% CI 0.61-0.97). No significant relationships were found for domestic PA and risk of CVD mortality.

*Walking*

Gregg et al. (50) investigated the relationship between walking and mortality in 2,896 adults with T2D who participated in the 1990-1991 NHIS. Three categories were created for

both walking (low: 0 hr/wk, moderate: 0-1.9 hr/wk, and high: ≥2 hr/wk). Following adjustment for age, gender, race, BMI, self-rated health, smoking, weight loss approaches, hospitalizations, hypertension and use of antihypertensive medications, physician visits, limitations caused by CVD and cancer, and level functional limitation, significantly lower risk for all-cause mortality was revealed in those who were categorized as high walking (HR 0.61, 95% CI 0.48-0.78). High walking was also associated with reduced CVD mortality risk (HR 0.66, 95% CI 0.45-0.96).

In the aforementioned analysis by Sadarangani et al. (56), investigators also examined the relationship between walking and both all-cause and CVD mortality. Walking was categorized into three levels (none, below median, above median) based on calculated MET-hrs/wk from reported time spent walking and pace (i.e. slow, average, brisk, or fast). Brisk and fast were considered moderate intensity. Those categorized as above median for walking had a significantly lower risk for all-cause mortality (HR 0.68, 95% CI 0.54-0.85). No relationship was found across categories of walking and CVD mortality.

Using data from the EPIC study, Sluik et al. (57) investigated the relationship between walking and all-cause mortality and CVD mortality in participants with T2D. Walking was categorized into quartiles by hr/wk (inactive, moderately inactive, moderately active, and active). Walking was only associated with lower risk for CVD mortality in moderately inactive (HR 0.40, 95% CI 0.22-0.74) and moderately active (HR 0.44, 95% CI 0.24-0.79) adults.

Smith et al. (58) examined the relationship between walking and CVD mortality in a group of adults with T2D from the Rancho Bernardo Study. Participants self-reported the volume of walking in miles/wk. Walking ≥1 mile/wk was associated with lower risk for all-cause mortality (HR 0.54, 95% CI 0.33-0.88). No associations were found for CVD mortality.

Using data from the Health Professionals' follow-up study, Tanasescu et al. (59) examined the association between PA and all-cause mortality in a sample of 3,058 men with T2D. Walking quintiles were created based on MET-hr/wk calculated from self-reported participation in PA. Only those in quintile 5 (≥16.1 MET-hrs/wk) of walking had a significant reduction in risk for all-cause mortality (HR 0.60, 95% CI 0.41-0.88).

*Summary of studies investigating physical activity and mortality in participants with diabetes*

The relationship between PA and all-cause or CVD mortality has been examined across several domains (Total, LTPA, occupational, transportational, domestic, and walking). It is evident from the literature presented there is a severe paucity of studies specifically for occupational PA (51), transportational PA (51) and domestic PA (56). Regarding total PA, LTPA and walking, a 2012 meta-analysis by Sluik et al. (57) summarized the results of several of the aforementioned studies (49-53, 55, 58, 60, 61). For analyses examining total PA, a significant summary effect was found for both all-cause (HR 0.60, 95% CI 0.49-0.73) and CVD (HR 0.58, 95% CI 0.50-0.66) mortality when comparing the most active to least active groups. For LTPA, significant summary effects were found for both all-cause (HR 0.64, 95% CI 0.57-0.72) and CVD (HR 0.64, 95% CI 0.51-0.80) mortality comparing the most active to least active groups. Walking (comparing the most active vs. least active) was associated with lower risk for all-cause (HR 0.68, 95% CI 0.59-0.78) and CVD (HR 0.59, 95% CI 0.46-0.76) mortality.

From the studies presented it is evident that PA is associated with a similar decreased risk for all-cause and CVD mortality, specifically in those with T2D. However, due to the vast differences in PA measurement, it cannot be determined the minimum dose needed to see significant risk reductions for mortality. Therefore, future research should focus on dose-response analysis structured around the 2008 DHHS aerobic PAG to determine minimum dose

required. Nonetheless, PA, especially total, LTPA and walking, are effective in reducing mortality risk in those with T2D.

**Physical activity and mortality in those with diabetes; effect modification by race/ethnicity**

One study (62) has examined the relationship between PA and mortality in those with T2D while subsequently examining the effect modification by race-ethnicity. One study (63) examined cardiorespiratory fitness and mortality. A 2015 study by Glenn et al. (62) examined the association between self-reported PA, sedentary time, and mortality among NHB and NHW adults from low-income households. Physical activity was categorized into quartiles based on calculated MET-hrs/d from self-reported time spent across several activities. Following adjustment for age, gender, BMI, income, education, history of comorbidities (hypertension, high cholesterol, myocardial infarction, and stroke), smoking, T2D characteristics (insulin use and time since diabetes diagnosis), and sedentary time, both NHBs and NHWs had significantly lower HRs for all-cause mortality across quartiles 2, 3, and 4 of PA compared to quartile 1 [NHW (2: HR 0.66, 95% CI 0.54-0.82, 3: HR 0.64, 95% CI 0.51-0.79, 4: HR 0.55, 95% CI 0.43-0.70); NHB (2: HR 0.83, 95% CI 0.73-0.95, 3: HR 0.68, 95% CI 0.59-0.79, 4: HR 0.69, 95% CI 0.60-0.80)]..

Kokkinos et al. (63) examined the relationship between cardiorespiratory fitness and all-cause mortality in a sample of male NHB and NHW adults with T2D. Tertiles of fitness were crated specific to the sample based on peak METs from a Bruce treadmill test. Following adjustment for age, BMI, blood pressure medications, statins, hypertension, dyslipidemia, smoking, and mortality in the first year of follow-up, significantly lower risk for mortality was found in NHBs who were in fitness tertiles 2 (RR 0.65, 95% CI 0.53-0.79) and 3 (RR 0.56, 95% CI 0.40-0.77). Similar results were found in NHWs in tertiles 2 (RR 0.57, 95% CI 0.544-0.73)

and 3 (RR 0.34, 95% CI 0.23-0.51).

The results of these studies indicate that there seems to be no effect modification of race-ethnicity on the relationship between PA and all-cause mortality in those with type 2 diabetes.

**Physical activity and diabetes-related mortality**

While there are many studies that have shown an inverse relationship between PA and mortality among those with T2D; only two studies (11, 12) have examined the relationship between PA and diabetes-related mortality. In addition, only a single study has examined cardiorespiratory fitness and diabetes-related mortality (61). For this section, diabetes-related mortality is defined as mortality related to any type of diabetes.

Using participants in the Danish Diet, Cancer, and Health study, Andersen et al. (11) examined the relationship between PA and diabetes-related mortality. Participants were 50-65 years of age and self-reported demographic information, dietary and health behaviors such as smoking, alcohol consumption and PA. Physical activity was assessed via questionnaire that asked about weekly hours spent participating in sports, cycling, gardening, walking, housework (cleaning), and household chores (house repairs). Physical activity was then dichotomized according to reported participation in sports, cycling, gardening or walking. Diabetes-related mortality was defined using the ICD-10 codes E10-E14. Following adjustment for air pollution, gender, calendar year, other PA, OPA, smoking status, smoking intensity, smoking duration, alcohol intake, environmental tobacco smoke, education, fruit and vegetable intake, fat intake, risk occupation, mean income in municipality, and marital status, those reporting any participation in sports (HR 0.34, 95% CI 0.21-0.55), cycling (HR 0.61, 95% CI 0.42-0.89), or gardening (HR 0.42, 95% CI 0.28-0.62) had significantly lower HRs for diabetes-related mortality compared to those reporting no participation. In those reporting walking, statistical

significance was not attained (HR 0.77. 95% CI 0.44-1.33).

Williams et al. (12) examined the relationship between MET-hrs/d of walking and mortality, including mortality from diabetes. Study participants were from the National Walker's Health Study. Participants reported demographic characteristics, dietary behaviors, health behaviors, medication use, and weekly walking participation (distance and average speed). Mortality was classified using the ICD-10 mortality codes. Walking (MET-hrs/d) was categorized into four categories: <1.07 (category 1), 1.07-1.8 (category 2), >1.8-3.5 (category 3), and ≥3.6 (category 4). Following adjustment for age, race, gender, education, prior heart attack, aspirin use, and intakes of red meat, fruit, and alcohol, those in category three (HR 0.36, 95% CI 0.18-0.73) and category four (HR 0.09, 95% CI 0.2-0.4) had significantly lower HRs for diabetes-related mortality compared to category one. Following further adjustment for medication use and baseline BMI, results remained significant for category four only (HR 0.17, 95% CI 0.04-0.73). In a separate analysis adjusting for reported BMI when started walking, a significant HR was found for category four (HR 0.17, 95% CI 0.04-0.80); with those in category three were trending towards significance (HR 0.41, 95% CI 0.16-1.03, p=0.06).

A separate survival analysis using the same sample from Williams et al. (12) examined if the HR for the underlying cause of death was changed when including risk from other causes. In other words, would risk for diabetes-related mortality change in someone whose underlying cause of death was not from diabetes. Following adjustment for covariates, medication use, and baseline BMI, those in categories three (HR 0.59, 95% CI 0.38-0.90) and four (HR 0.41, 95% CI 0.23-0.71) had significantly lower HRs for mortality from diabetes compared to category one. When adjusting for BMI, results remained significant. These results indicate that despite diabetes not being the primary cause of death, higher volumes of walking are significantly associated with

a lower risk for diabetes-related mortality.

In an analysis of 1,188 men with T2D from the ACLS, Wei et al. (61) examined the relationship between fitness and diabetes-related mortality. Following adjustment for age, examination year, smoking, alcohol, baseline cardiovascular disease, family history of CVD, high cholesterol, diabetes status, glucose level, high blood pressure, and overweight status, those who were classified as unfit had a significantly greater risk for death from diabetes (RR 7.4, 95% CI 1.4-39.6) compared to those who were fit.

It is evident from the presented studies that an inverse relationship exists between PA and the risk of diabetes-related mortality. Andersen et al. (58) revealed significant protection from diabetes-related mortality in those reporting sports, cycling, gardening or walking; indicating that different types of PA can protect against diabetes-related mortality. Williams et al. (59) revealed that ≥3.6 MET-hrs/d of walking was significantly associated with lower risk for diabetes-related mortality independent of several important covariates including race. Moreover, walking was significantly associated with reduced risk for diabetes as a secondary cause of death independent of race. Cardiorespiratory fitness was also found to be significantly associated with increased risk for diabetes-related morality in those who were unfit compared to fit.

**Summary**

Diabetes (the vast majority being T2D) is a complex, deleterious metabolic disease that is reaching epidemic proportions in the U.S. Currently, the prevalence estimates range from 9.3% (13, 14) to 14.5% (15). More importantly, the prevalence of diabetes is consistently higher among minority groups when compared to NHWs, independent of the survey method and diagnostic criteria used.

It is well established there is an inverse association between PA and risk of T2D. These

results were further extended by Boyer et al. (10) (appendix 2); who examined the effect modification of race-ethnicity on this relationship. When comparing the most to the least active, significant and similar risk reductions were seen in all race-ethnic groups (NHW, Asians, Hispanic, and American Indian) with the exception of NHB. Several mechanisms were postulated by Boyer et al. (10) (appendix 2) to provide physiological rationale for the results seen.

The relationship between PA and mortality in those with T2D is well established, with an inverse association being found across most studies. When examining the effect modification of race-ethnicity on this relationship, the two studies examined reveal a more pronounced reduction in mortality risk in NHWs compared to NHBs. However, more research is needed. Specific to diabetes-related mortality, only two studies have been conducted examining PA and risk. Moreover, these studies did not examine this relationship specific to different race-ethnic groups. Knowing that PA does not reduce the risk for T2D equally across race-ethnicity (specifically NHB), it is necessary to further extend the body of literature to diabetes-related mortality.

# PART 3

# METHODOLOGY

The purpose of this study was to examine the effect modification of race-ethnicity on the association between PA and diabetes-related mortality in two nationally representative samples of U.S. adults. The study will utilize data from both the National Health and Nutrition Examination Survey (NHANES) III and the 1999-2006 continuous NHANES that are linked to the National Death Index (NDI). The following section provides a detailed description of the methodology to be used for this study including: a description of the participants, the methodology behind NHANES data collection, a description of the NDI and linkage to NHANES, a description of the variables of interest, and data analysis.

**Participants**

The participants included in this study participated in either the NHANES III or the 1999-2006 NHANES and are described below.

*NHANES III*

The study participants for all analyses in research question 1, using the NHANES III, will meet the following inclusion criteria:

- Adults 20-79 years of age. 79 years was chosen as the upper end cutpoint for age as previous research has shown that the role of diabetes becomes ambiguous in its contribution to mortality at higher ages (32).
- Did not die within the first three years of follow-up. Within the NHANES III, the cut off of three years has been previously used (12).
- Completed testing at the mobile examination center (MEC).
- Had complete data for all variables of interest.
- If female, were not pregnant or lactating.

*1999-2006 NHANES*

The study participants for all analyses for research questions 2A-2C using the 1999-2006 NHANES met the following inclusion criteria:

- Adults 40-79 years of age. 79 years was chosen as the upper end cutpoint for age as previous research has shown that the role of diabetes becomes ambiguous in its contribution to mortality at higher ages (32).
- Completed testing at the mobile examination center (MEC).
- Had complete data for all variables of interest.
- If female, were not pregnant or lactating.

The age-range for research questions 2A-2C has been previously used in a continuous NHANES mortality analysis (64). Due to the vast majority of diabetes diagnoses occurring between the ages of 40 and 64 years (65) and the prevalence of those below 40 being low (65), we elected to use the age cutoff of 40-79 years of age.

**NHANES data collection**

The NHANES studies, conducted by the National Center for Health Statistics (NCHS) , began forty-one years ago in 1976 and were designed to provide population based estimates of health, health behaviors and disease via a representative sample of the U.S. (66). Several cycles of the NHANES have been conducted; beginning in 1976 with the first phase (NHANES I) (67). NHANES II was conducted between 1976 and 1980 (67). NHANES III was conducted in two phases; the first from 1988 to 1991 and the second form 1991 to 1994 (68). Beginning in 1999, the NHANES moved to a continuous two-year cycle with a focus on emerging health issues within the U.S. (69).

The NHANES is cross-sectional in nature and uses a complex, multi-stage sampling design to obtain its participants (70). Furthermore, all participants are non-institutionalized residents within the 50 states or the District of Columbia and over the age of two months. The stages of sampling are broken into four parts (70). The first is the selection of primary sampling units (PSUs), which are usually single counties but are sometimes combined, adjacent counties to ensure the PSU's meet the minimum population size requirement (68). The second stage is characterized by dividing the PSUs into segments the size of a city block. The third stage is characterized by a random sampling of households within the divided segments. A component of the NHANES is the oversampling of minority groups (i.e. African Americans, adolescents [12-19 years], and adults ≥60 years of age) to ensure adequate representation within the sample (70). Within stage 3 of the sampling methods, a higher probability exists for sampling in regions where oversampled participants reside. Stage four is characterized by randomly selecting at least one participant from each household selected.

Within the NHANES, several different assessments and measurements are conducted. All NHANES participants are assessed via the household interview in which demographic characteristics, socioeconomic status, self-reported health behaviors, and health issues are collected (66). A subsample of participants undergo a detailed health examination and laboratory tests at the MEC in which several physiological variables are measured such as blood pressure, cardiorespiratory fitness and glycosylated hemoglobin (HbA1c) (66, 71).

**National Death Index Data Linkage**

The National Death Index (NDI) is a national database run by the NCHS that maintains the records of all U.S. deaths starting in 1979 (72). From the data available at the NDI, it is possible to link those records to participants within NCHS surveys, such as the NHANES, using

the identifying information (such as name, social security number, gender, race, and marital status) (72). Death records are then matched to NHANES data based upon seven specific criteria (72):

> "1. Social Security Number (SSN)"
>
> "2. First and last name, exact month of birth, year of birth within 1 year"
>
> "3. Last name, first initial and middle initial, exact month of birth, year of birth within 1 year"
>
> "4. First and last name, exact month of birth, exact day of birth"
>
> "5. Last name, first initial and middle initial, exact month of birth, exact day of birth"
>
> "6. First name, father's surname, exact month of birth, exact year of birth"
>
> "7. For females only, first name, exact month and year of birth, and last name from the survey record matching birth surname on the NDI record (for females who change their name after marriage but don't supply a birth surname)"

Death records matching with survey data are then scored on a 1-5 "class" scale to assess the strength of matching (72). The class scale taken from the NDI documentation is as follows (72):

> "Class 1: Agreed on at least 8 (of 9) or 4 (of 4) digits of SSN, first name, middle initial, last name birth year (+/- 3 years), birth month, sex, and state of birth"
>
> "Class 2: Agreed on at least 7 (of 9) or 4 (of 4) digits of SSN at least 5 more of the following items: first name, middle initial, last name, birth year (+/- 3 years), birth month, sex, and state of birth."

"Class 3: There were two types of Class 3 matches:"

> "Type A: SSN is unknown, but last name matched and at least 7 of the following items agreed: first name, middle initial, last name, birth year (+/- 3 years), birth day, sex, race, marital status and state of birth."
>
> "Type B: Records in this category were initially put in Class 5 but switched to Class 3 if after review, there was the possibility that SSN was either recorded incorrectly or that the spouse's SSN was recorded instead of the subject's SSN. In this category, SSN was known but 3 or more (of 9) and 1 or more (of 4) digits did not agree, but at least 8 of the following items agreed: first name, middle initial, last name, birth year, birth day, sex, race, marital status, and state of birth. All total scores were adjusted to reflect the final class code for the potential matches. For example, any record that was switched from Class 5 to Class 3 had its score adjusted to reflect that SSN is missing, with the value of 0 assigned to SSN."

"Class 4: SSN was unknown on either the NCHS survey submission record or the NDI record and fewer than 8 of the items listed in Class 3 matched."

"Class 5: SSN was present but fewer than 7 (of 9) or 4 (of 4) digits on SSN agreed."

Following class scoring, all class 1 records were included; and record classes 2-4 used a specific cut-off point to clarify true matches (72). Those who did not meet class 1 or the specific criteria for classes 2-4 were considered no matches and were thus de-identified. Specific to NHANES, participants with matched NDI records were linked by their respondent sequence number (SEQN), which is the individual identifier variable within the NHANES datasets found within

the demographic file. The public-release version of the NDI mortality records (73) were used to merge and link the NHANES individual records by SEQN in both the NHANES III and the 1999-2006 NHANES components of the current study.

**Measures**

The following section details the variables used.

Effect Modification: Race/Ethnicity

All analyses were stratified by race-ethnicity to answer all research questions. Race-ethnicity, contained with the demographic data files, will be categorized and defined by the variables DMARETHN (NHANES III) and RIDRETH1 (1999-2006 NHANES) which uses four categories to classify race-ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American and Other). For analyses in NHANES III, non-Hispanic white, non-Hispanic Black, and Mexican American were used. For the 1999-2006 NHANES, non-Hispanic white and non-Hispanic Black were used.

Dependent Variable: Diabetes-related mortality

The dependent variable in this study was diabetes-related mortality obtained from the NDI. The public-use mortality codes available are derived from the restricted-use mortality files which provides detailed information about causes of death (73) (Appendix 1, table 2). From this list, mortality from many different diseases is recoded into all-encompassing diseases such as disease of the heart or malignant neoplasms (Appendix 1, table 2) (73). This allows for a more general examination of mortality from a population-based standpoint and ensures that no sensitive information is attained from the study participants. Furthermore, within the linked-mortality data, to ease statistical analysis across multiple years or data sets, all causes of death

codes before 1999 (International Statistical Classification of Diseases, Injuries, and Causes of Death [ICD-9]) were recoded to match the ICD-10 causes of death.

For research questions 1-2C, diabetes-related mortality was determined from the public-use mortality data files using the ICD-10 (E10-E14) codes (73). Table 1 in appendix 1 provides the descriptions of each ICD-10 code used to classify diabetes mortality. In order to include those who had diabetes as an underlying or non-primary cause, diabetes-related mortality was defined as either death from diabetes mellitus or if diabetes was flagged on the death certificate with multiple causes of death.

Primary independent variables: Self-Report and Accelerometer Physical Activity

Physical activity was the primary independent variable in the analyses. Several different measures of PA were used across the research questions depending upon the specific year and cycle of NHANES.

*NHANES III (Self-Reported Physical Activity)*

The following describes the methodology used to classify and categorize PA for research question 1 specific to NHANES III. Within the NHANES III, intensity and frequency of 13 possible leisure-time activities were reported. Leisure-time PA (LTPA) was assessed via questionnaire inquiring about participation in eight specific aerobic activities (walking, running/jogging, cycling, swimming, aerobics, calisthenics, swimming, and lawn work/gardening) (68). Furthermore, four open-ended PA questions were also asked to assess activity beyond the nine specific activity questions. The intensity of each activity, denoted by a specific metabolic equivalent (MET), was defined and classified according to the Compendium of Physical Activities (74). One MET is defined as 3.5 ml/kg/min and equates to the energy cost

of rest (75). Participants also self-reported the monthly frequency of each activity reported. Duration was not assessed in the NHANES III PA component. Furthermore, activity associated with lifting weights was excluded as the study purpose was specifically examining aerobic PA.

The primary independent variable in this study was a three category, physical activity guideline index (PAGI); using the 2007 PA guidelines (76) as the criteria for meeting the recommendations (≥ 5 d/wk of moderate-intensity PA or ≥3 d/wk of vigorous-intensity PA). Initially, each reported activity was categorized into one of five intensity categories based upon the age-specific MET cut-points in the 1996 Surgeon General's Report on Physical Activity and Health (77)(appendix 4). Categories were adjusted based on the relative intensities for the following age groups: 20-39, 40-59, and 60-79. The five categories were as follows: very light (level 1), light (level 2), moderate (level 3), hard (level 4), and very hard (level 5). Intensity levels 2 and 3 were classified as moderate-intensity activity; intensity levels 4 and 5 were classified as vigorous-intensity activity. The weekly frequency for each activity (calculated by dividing the monthly frequency by 4.3) was multiplied by its coinciding relative-intensity activity level (1-5); creating a physical activity score (PAS) for each individually reported activity. The individual PAS were then summed to create an age-adjusted overall total PAS.

The three categories for the PAGI are as follows: inactive, insufficiently active, and active. Inactive was defined as a total PAS of 0 or those who's PAS only included "very light" activity. Across the 13 potential activities reported, only 10 participants reported only "very light" activity. Thus, they were categorized as inactive. Insufficiently active was defined as a total PAS ranging between >0 and <10. Active was defined as a PA score of ≥10. The cutoff of 10 was used as it is a proxy cutoff that equates to 5 bouts/wk of moderate-intensity activity (78, 79). For the purpose of the PAGI, bouts were assumed to be reflective of days/week (d/wk). For

example: The NHANES III MET value associated with the walking question was 3.5 METs. In an adult aged 38, this would categorize them into PA intensity level 2; which would be considered a moderate-intensity activity (see appendix 4) for that age-group. If at least 5 d/wk of walking are reported then this participant would be classified as active (i.e. PA intensity level 2 x 5 d/wk = PA score 10).

*1999-2004 NHANES (Self-Reported Physical Activity)*

The following details the methodology that will be used to classify and categorize PA for research question 2A. Self-reported LTPA, transportational PA and domestic PA over the past month were assessed with data being reported in two data files -- the Physical Activity Questionnaire (PAQ) and the PA individual activities file (PAQIAF)(80). Data from these files provide the following information specific to 43 different activities: type, frequency (times per week), and duration (minutes per bout) for each activity. A MET score will be calculated and assigned for each activity as well (81). From these variables MET-minutes per week will be calculated for three domains: LTPA, transportational PA and domestic PA. A summary MET-minute score will then be calculated by adding the total MET-minutes from each domain. From the total MET-minutes variable, two different classification methods will be used to examine the dose-response association between PA and diabetes-specific mortality. The first is the creation of age-adjusted, sample-specific PA MET-minutes quintiles. This method has been used in previous NHANES analyses (82). The second method will directly examine the association between PA and diabetes-specific mortality using the 2006 Department of Health and Human Services (DHHS) aerobic PA guideline (33). Three categories will be created: 0 MET-minutes/wk (Inactive), <500 MET-minutes/wk (Irregular PA), 500-999 MET-minutes/wk which equates to meeting the 2008 DHHS aerobic PA guidelines of 150 minutes of MVPA/wk, and ≥1000 MET-

minutes/wk which equates to volumes exceeding the recommendations of ≥300 minutes/wk of MVPA. This method has also been used in past studies (83, 84).

*2003-2006 NHANES (Objective Physical Activity)*

The following details the methodology, specific to accelerometer-measured PA, to be used to classify and categorize PA for research questions 2B and 2C. Within the 2003-2006 NHANES, accelerometer data was collected using an ActiGraph model 7164 accelerometer. Participants were instructed to wear the accelerometer on the right hip for seven consecutive days and to remove the accelerometer when participating in water activities such as bathing or swimming as well as sleeping (85). A valid day of wear time was defined as ≥10 hours of wear time per day (86). In order to be utilized in the analysis, at least four days of valid wear time were needed, with ≥60 minutes of zero accelerometer counts defined as non-wear time. Two different common cutpoints (87) will be used to quantify minutes spent in MVPA per day; ≥2020 counts per minute (cpm) (86) and ≥760 cpm (88). Minutes to be included in the analyses reflected all minutes spent above the MVPA thresholds.

To answer research question 3A, the dose-response relationship between PA and diabetes-related morality will be examined for every 10 minutes of moderate-to-vigorous PA (MVPA) accumulated per day. This incremental 10 minute increase in MVPA has been used in previous analysis (89).

To examine the dose-response relationship between PA and diabetes-related mortality as mentioned in research question 3B, we will use the Wolff-Hughes et al. (90) population-referenced total activity count/day (TAC/d) percentiles. Briefly, the “activity counts” utilized in this analysis are a reflection of what the accelerometer actually measures, and are created by filtering, full-wave rectifying and integrating the raw acceleration across the 1-minute epochs.

The TAC/d variable was specifically created by summing up the total activity counts and dividing them by the number of valid wear days (42). These percentiles are demarcated at the $5^{th}$, $10^{th}$, $25^{th}$, $50^{th}$, $75^{th}$, $90^{th}$, $95^{th}$ and $97^{th}$ percentiles. From these percentiles, quartiles ($25^{th}$, $50^{th}$ and $75^{th}$) will be used to examine a more precise dose-response relationship and to ensure sufficient power across quartiles.

Covariates

Several potential confounding measures will be used as covariates in this study. The following list details the covariates used in the study:

- Age: Age was examined continuously.
- Gender: Categorized as male or female.
- Education: Four categories of education will be used: < high school, high school graduate, some college and college graduate.
- Family history of diabetes: A family history of diabetes is linked to increased risk for T2D and, thus, an increased risk for diabetes-related mortality (91). Participants self-reported family history of diabetes will be dichotomized as either yes or no. The 2005-2006 NHANES removed the family history questions specific to diabetes, therefore the 2003-2006 analyses did not include family history as a covariate.
- Smoking: Smoking will be categorized as either current smoker, previous smoker, or non-smoker based on self-report.
- Alcohol consumption: Previous research has shown alcohol consumption to be inversely associated with the risk of T2D (92) and, thus, could be linked to diabetes-related mortality. For NHANES III, alcohol consumption was categorized as either non-drinker or drinker by responding yes or no to the question “In the past 12 months did you

MAPE2 have at least 12 drinks of any kind of alcoholic beverage". For the 1999-2004 NHANES, a three-level categorical variable will be used to categorize alcohol consumption based on the United States Department of Agriculture (USDA) and DHHS gender specific cut-points (93): non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).

- Glycemic Index: A three-category variable was created based on the current American Diabetes Association glycosylated hemoglobin (HbA1c) recommendations (13) to establish euglycemic (HbA1c <5.7%), those with pre-diabetes (HbA1c 5.7 - <6.5%), and those with diabetes (HbA1c ≥6.5%).
- Body mass index (BMI): BMI will be examined as a continuous variable
- The Healthy Eating Index (HEI): The HEI is a quantitative reflection of overall dietary quality and has been validated for use in the NHANES (94). The HEI is based upon 10 dietary components that are summed on a 0-100 scale; the higher the score being indicative of a better dietary quality (95). HEI will be examined continuously.

**Data analysis**

All analyses were conducted using SAS 9.4 (96), which allows for the incorporation of the sampling weights in the multi-staged, complex sampling design inherent to NHANES. Sampling weights are used in analyses to account for the complex survey design, oversampling of certain groups, non-response, and post-stratification (97). These weights are utilized to ensure the correct representative sample is used in analyses.

For NHANES III, sampling weights are provided and are used based upon the sample

participant characteristics and variables in the analysis (68). For the current study, due to use of variables from the household interview and MEC examination, the final MEC weight (WTPFEX6) will be used (68). For the continuous NHANES, 2-year sampling weights for the interview, MEC and fasted laboratory files are provided by the NCHS. These weights can be combined and calculated based on the cycles used (97). For the current study, a fasted 6-year weight will be created for analyses using the 1999-2004 NHANES by combining the 4-year sampling weights from the 1999-2002 NHANES and the 2-year fasted weights from the 2003-2004 NHANES. For analyses utilizing the 2003-2006 NHANES, a similar method was employed by combining the fasted weights from the 2003-2004 NHANES and the 2005-2006 NHANES.

Statistical Analysis

SAS 9.4 (96) was used to manage all data inclusive of all complex variable recodes and to validate recoding. Weighted prevalence estimates were generated using PROC SURVEYFREQ. All research questions were analyzed using two SAS survival analysis features: PROC LIFETEST and PROC SURVEYPHREG. PROC LIFETEST was used to estimate the survivorship related to diabetes-related mortality via Kaplan-Meier (KM) curves. Specific KM curves were generated across race-ethnic groups as well as the PA variables for the NHANES III and the 1999-2004 NHANES. Furthermore, KM curves were created across the PA variables specific to each race-ethnic group. PROC SURVEYPHREG was used to test the null hypothesis that the individual Cox proportional hazard ratios are equal to 1 across PA measures within each race-ethnic group. This procedure allows for the incorporation of sampling weights inherent with the sampling design of NHANES. For all four research questions two models were created: unadjusted and fully adjusted using the aforementioned covariates.

# PART 4

# EFFECT MODIFICATION OF THE ASSOCIATION BETWEEN LEISURE-TIME AEROBIC PHYSICAL ACTIVITY AND DIABETES-RELATED MORTALITY BY RACE-ETHNICITY: NHANES III

**Abstract**

**Purpose:** To examine potential effect modification by race-ethnicity of the relationship between physical activity (PA) and diabetes-related mortality risk using a sample of U.S. adults from the Third National Health and Nutrition Examination Survey (NHANES III). **Methods:** The sample (n=10,717) included adults (≥20 years) who attended the Mobile Examination Center (MEC). An age-standardized PA score (PAS) was calculated from the self-reported frequency and intensity of 12 leisure-time aerobic activities. The PA scores were then grouped into three categories: inactive (PAS = 0), insufficiently active (PAS >0 - <10), and active (PAS ≥10). A PAS of 10 was chosen as a proxy cutoff for 5 bouts/wk of moderate-intensity activity, the 2007 American Heart Association/American College of Sports Medicine aerobic PA guideline. Diabetes-related mortality was defined as either death from diabetes mellitus as the primary cause or if diabetes was flagged on the death certificate as a contributing cause. Race-ethnic groups included: non-Hispanic white (NHW), non-Hispanic black (NHB), and Mexican American (MA). SAS 9.4 survey procedures were used for all statistical analyses. **Results:** There was no interaction between PA and race-ethnicity (p=0.83). Compared to inactive NHW, there was a significantly lower risk for diabetes-related mortality for insufficiently active (Hazard Ratio [HR] 0.51, 95% Confidence Interval [CI] 0.29-0.89) and active (HR 0.57, 95% CI 0.33-1.00) NHW adults. Statistical significance was not achieved for any level of activity for NHB and MA. A significant p-for-trend was revealed only for MA. **Conclusions:** The results of this study suggest that accumulation of any volume of PA is associated with a significantly lowered risk for diabetes-related mortality only in NHW. A significant dose-response relationship was only observed among MA. However, the interaction between race-ethnicity and PA did not attain statistical significance. Thus the presence of effect modification could not be determined from the current

study, but further investigation is warranted. Given longer follow-up time in the NHANES III cohort, the ability to estimate more precise risk reductions will become plausible.

## Introduction

Diabetes is a deleterious metabolic condition characterized by chronic hyperglycemia. Currently, diabetes is the seventh leading cause of mortality among adults in the United States (U.S.)(approximately 2.8% of all deaths); with the vast majority of these deaths being related specifically to type 2 diabetes (1, 2, 32). Despite being a top ten cause of death, diabetes is more likely to be a contributing cause of death rather than the primary cause of death; accounting for approximately 10.8% of deaths (2, 3, 32). Using data from the 1997-2009 National Health Interview Survey (NHIS) and the 1999-2010 National Health and Nutrition Examination Survey (NHANES), Stokes and Preston (32) found the population-attributable fraction (PAF) of death from diabetes was approximately 11.5%; suggesting that diabetes is the third leading cause of death in U.S. adults. Considering its strong link to cardiovascular disease (4, 5), cancers (6), kidney disease (7), and stroke (8); it is evident that diabetes plays a substantial role in mortality related to cardiovascular and metabolic causes.

The current mortality rates associated with diabetes differ across race-ethnic groups (1). The age-adjusted mortality rate attributable to diabetes is higher among Hispanics (25.1 per 100,000) and non-Hispanic blacks (NHB) (38.2 per 100,000) compared to those who are non-Hispanic white (NHW) (18.6 per 100,000) (1). Moreover, compared to NHW, NHB and Hispanics are 2.3 and 1.5 times more likely to die from diabetes, respectively (1). In the aforementioned analysis by Stokes and Preston (32), the percent of deaths from diabetes as the primary cause, as well as a contributing cause, were significantly higher in NHB and Mexican Americans (MA) compared to NHW. However, the PAFs were not statistically different across groups despite NHW having a 2% lower PAF. Given the clear disparities between race-ethnic groups, understanding how different preventive health behaviors, such as physical activity (PA), relate to diabetes-related mortality risk is of critical importance.

A recent meta-analysis by Boyer et al. (10) examined the effect modification of race-ethnicity on the relationship between aerobic PA and incidence of type 2 diabetes. When comparing the most active to the least active groups, a significant summary protective effect was found for NHW, American Indians, Asians, and Hispanics. No significant reduction in risk was found for NHB. Furthermore, when conducting a sensitivity analysis, the significant summary effect of PA was eliminated in Hispanics. Knowing the clear link between diabetes incidence and risk of diabetes-related mortality, it is hypothesized that the results of Boyer et al. (10) could translate to diabetes-related mortality.

Currently, only two studies have investigated the relationship between PA and diabetes-related mortality (11, 12). Using data from the Danish Diet, Cancer, and Health Cohort, Andersen et al. (11) found that any participation in sports (Hazard ratio [HR] 0.34, 95% CI 0.21-0.55), cycling (HR 0.61, 95% CI 0.42-0.89), or gardening (HR 0.42, 95% CI 0.28-0.62) resulted in significantly lower HRs for diabetes-related mortality compared to those reporting no participation in these activities. In those reporting walking, statistical significance was not attained (HR 0.77. 95% CI 0.44-1.33). Due to the relatively homogenous sample of white individuals, race-ethnicity was not controlled for. In the second study, Williams et al. (12) examined the relationship between daily MET-hours (MET-hrs/d) of self-reported walking and diabetes-related mortality using data form the National Walkers' Health Study. MET-hrs/d of walking were categorized into four levels: <1.07 MET-hrs/d (category 1), 1.07-1.8 MET-hrs/d (category 2), >1.8-3.5 MET-hrs/d (category 3), and ≥3.6 MET-hrs/d (category 4). Only those in category 4 (HR 0.17, 95% CI 0.04-0.80) had a significant reduction in risk for diabetes-related mortality. All analyses were adjusted for race-ethnicity; however effect modification was not examined. While these two studies reveal an inverse relationship between PA and diabetes-

related mortality, there currently exists no literature examining this relationship with attention to the possible effect modification within race-ethnicity.

The NHANES and the available National Data Index (NDI) linked data, provide a population based opportunity to examine the extent to which PA protects against diabetes-related mortality across several race-ethnic groups. Therefore, the purpose of this study was to examine the effect modification of race-ethnicity on the association between PA and diabetes-related mortality using data from the NHANES III and the NDI. It is hypothesized that similar doses of aerobic PA will not lead to similar risk reductions for diabetes-related mortality when comparing NHW to NHB and MA.

## Methods

### *Participants*

The present study utilized data from the NHANES III (1988-1994) (98). The NHANES is a cross-sectional survey conducted by the National Center for Health Statistics (NCHS) that utilizes a complex, multistage sampling design to provide a representative sample of the non-institutionalized U.S. population. Within the NHANES III, several different assessments and measurements were conducted. All NHANES III participants underwent a household interview in which demographic characteristics, socioeconomic status, self-reported health behaviors, and health issues were self-reported (66). A subsample of participants underwent a detailed health examination and laboratory test at a mobile examination center (MEC) in which several physiological variables were measured such as glycosylated hemoglobin (HbA1c) (66, 71).

For the present study participants met the following inclusion criteria: 1) adults 20-79 years of age (79 years was chosen as the upper end cutoff for age as previous research has shown that the role of diabetes becomes ambiguous in its contribution to mortality at higher ages (32));

2) did not die within the first three years of follow-up to reduce the potential effects of residual confounding from other chronic diseases; 3) completed testing at the MEC; 4) had complete data for all variables of interest; and 5) if female, were not pregnant or lactating. The total sample for the current study was 10,717 participants at baseline.

*Physical activity*

Within the NHANES III, intensity and frequency of 12 possible leisure-time activities were reported. Leisure-time PA (LTPA) was assessed via questionnaire inquiring about participation in eight specific aerobic activities (walking, running/jogging, cycling, swimming, aerobics, calisthenics, swimming, and lawn work/gardening) (68). Furthermore, four open-ended PA questions were also asked to assess activity beyond the eight specific activity questions. The intensity of each activity, denoted by a specific metabolic equivalent (MET), was defined and classified according to the Compendium of Physical Activities (74). One MET is defined as 3.5 ml/kg/min and equates to the energy cost of rest (75). Participants also self-reported the monthly frequency of each activity reported. Duration was not assessed in the NHANES III PA component. Furthermore, activity associated with lifting weights was excluded as the study purpose was specifically examining aerobic PA.

The primary independent variable in this study was a three category, physical activity guideline index (PAGI); using the 2007 PA guidelines (76) as the criteria for meeting the recommendations (≥ 5 d/wk of moderate-intensity PA or ≥3 d/wk of vigorous-intensity PA). Initially, each reported activity was categorized into one of five intensity categories based upon the age-specific MET cut-points in the 1996 Surgeon General's Report on Physical Activity and Health (77)(appendix 4). Categories were adjusted based on the relative intensities for the following age groups: 20-39, 40-59, and 60-79. The five categories were as follows: very light

(level 1), light (level 2), moderate (level 3), hard (level 4), and very hard (level 5). Intensity levels 2 and 3 were classified as moderate-intensity activity; intensity levels 4 and 5 were classified as vigorous-intensity activity. The weekly frequency for each activity (calculated by dividing the monthly frequency by 4.3) was multiplied by its coinciding relative-intensity activity level (1-5); creating a physical activity score (PAS) for each individually reported activity. The individual PAS were then summed to create an age-adjusted overall total PAS.

The three categories for the PAGI are as follows: inactive, insufficiently active, and active. Inactive was defined as a total PAS of 0 or those whose PAS only included "very light" activity. Across the 12 potential activities reported, only 10 participants reported only "very light" activity. Thus, they were categorized as inactive. Insufficiently active was defined as a total PAS ranging between >0 and <10. Active was defined as a PA score of ≥10. The cutoff of 10 was used as it is a proxy cutoff that equates to 5 bouts/wk of moderate-intensity activity (78, 79). For the purpose of the PAGI, bouts were assumed to be reflective of days/week (d/wk). For example: The NHANES III MET value associated with the walking question was 3.5 METs. In an adult aged 38, this would categorize them into PA intensity level 2; which would be considered a moderate-intensity activity (see appendix 4) for that age-group. If at least 5 d/wk of walking are reported, this participant would be classified as active (i.e. PA intensity level 2 x 5 d/wk = PA score 10).

*Diabetes-related mortality*

The dependent variable of interest was diabetes-related mortality. The NCHS linked death records from the National Death Index (NDI) to the NHANES participants' sequence numbers in NHANES via a process outlined elsewhere (72)(Chapter 3). Within those who were deceased, cause of death was determined and classified using the International Statistical

Classification of Diseases, Injuries, and Causes of Death (ICD)-10 codes. Diabetes-related mortality was determined from the public-use mortality data files using the ICD-10 codes E10-E14 (73). In order to include those who had diabetes as an underlying or non-primary cause, diabetes-related mortality was defined as either death from diabetes mellitus or if diabetes was flagged on the death certificate with multiple causes of death.

*Covariates*

Several potential confounding measures were used as covariates in this study. The demographic covariates included: age (examined continuously), gender (categorized as male or female), education (< high school, high school graduate, or some college/college graduate), and family history of diabetes (yes or no). Health behavior covariates included: self-reported smoking (current smoker, previous smoker, or non-smoker), alcohol consumption (categorized as either drinker or non-drinker by responding yes or no to the question "In the past 12 months did you have at least 12 drinks of any kind of alcoholic beverage"), and the Healthy Eating Index (HEI). The HEI is a quantitative reflection of overall dietary quality and has been validated for use in the NHANES (94). The HEI is based upon 10 dietary components that are summed on a 0-100 scale; the higher the score being indicative of a better dietary quality (95). HEI was examined continuously. Metabolic covariates included: glycemic index (a three-category variable based on the current American Diabetes Association HbA1c recommendations (13) to establish euglycemia (HbA1c <5.7%), those with pre-diabetes (HbA1c 5.7 - <6.5%), and those with diabetes (HbA1c ≥6.5%)), and body mass index (BMI) (examined continuously).

*Statistical analysis*

All variable recodes and analyses were conducted using SAS 9.4 (96), which allows for the incorporation of the sampling weights to account for the complex survey design,

oversampling of certain groups, non-response, and post-stratification inherent to NHANES (97). These weights are utilized to ensure the correct representative sample is used in analyses.

Weighted prevalence estimates were generated using PROC SURVEYFREQ. PROC LIFETEST was used to estimate the survivorship related to diabetes-related mortality via weighted Kaplan-Meier curves. Specific Kaplan-Meier curves were created across the PA variables specific to each race-ethnic group. PROC SURVEYPHREG was used to test the null hypothesis that the individual Cox proportional hazard ratios (HR) are equal to 1 across PA measures within each race-ethnic group. This procedure allows for the incorporation of sampling weights inherent with the sampling design of NHANES. Two specific analyses were conducted. The first examined the relationship between PA and diabetes-related mortality using race-ethnicity as a controlling covariate. Within this analysis, the interaction between race-ethnicity and the PAGI was tested. The second examined the same relationship stratifying by race-ethnicity. Two models were used across the two specific analyses:  unadjusted and fully adjusted using the aforementioned covariates.

**Results**

Table 4.1 provides the demographic, health behavior and physical activity characteristics of the total study sample and specific to race-ethnicity. Compared to NHW, NHB and MA were younger, had a significantly higher prevalence of diabetes and family history of diabetes. Regarding PA participation, NHB and MA had a significantly lower median PAS score and had a higher prevalence of inactive participants.

Table 4.2 provides the diabetes-related mortality characteristics of the total study sample and specific to race-ethnicity. Compared to NHW, NHB and MA had a significantly younger baseline age when examined at the MEC as well as a significantly younger age in which mortality occurred. Compared to NHW, NHB and MA had a higher age-adjusted mortality rate per 10,000 person years.

Figures 4.1, 4.2, and 4.3 illustrate the weighted, unadjusted Kaplan-Meier survival probability curves across the PAGI for each race-ethnic group. Across all race-ethnic groups the poorest survival probability was in inactive participants.

Table 4.3 illustrates the results of the Cox proportional hazards model examining the relationship between the PAGI and diabetes-related mortality in the total sample. In model 2 (adjusted for age and race-ethnicity), a significant reduction in the hazard for diabetes-related mortality was found for those who were categorized as either insufficiently active (HR 0.46, 95% CI 0.31-0.67) or active (HR 0.35, 95% CI 0.23-0.53). For model 2, the p-for-interaction between race-ethnicity and the PAGI was p=0.44. Following further adjustment for other covariates (model 3) results remained significant, but attenuated (insufficiently active [HR 0.54, 95% CI 0.34-0.86], active [HR 0.58, 95% CI 0.36-0.94)]. For the fully-adjusted model 3, the p-for-interaction between race-ethnicity and the PAGI was p=0.83.

Table 4.4 displays the results of the Cox Proportional HR analyses of the PAGI with diabetes-related mortality stratified by race-ethnicity. In the unadjusted analysis, NHWs categorized as insufficiently active (HR 0.30, 95% CI 0.18-0.48) or active (HR 0.26, 95% CI 0.16-0.43) had significantly lower risk for diabetes-related mortality. In the unadjusted analysis for NHBs, significantly lower risk for diabetes-related mortality was found for those who were either insufficiently active (HR 0.44, 95% CI 0.26-0.75) or active (HR 0.27, 95% CI 0.12-0.58). In the unadjusted analysis in MA, only those categorized as active had a significantly lower risk for diabetes-related mortality (HR 0.32, 95% CI 0.17-0.60). In the fully-adjusted analysis, only insufficiently active (HR 0.51, 95% CI 0.29-0.89) and active (HR 0.57, 95% CI 0.33-0.99) NHWs had a significant reduction in risk for diabetes-related mortality. In NHB and MA, no significant risk reductions were found for the PAGI and diabetes-related mortality following further adjustment for all covariates. Linear trend analysis found only MA having a significant inverse trend across categories of the PAGI for diabetes-related mortality (p=0.04).

Table 4.1. Demographic, heath, mortality, and physical activity characteristics of the participants: NHANES III (N=10,717)

| Variables | Value[b] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | RACE-ETHNICITY | | | | | | |
| | Total | | NHW (N=4563) | | NHB (N=3057) | | MA (N=3097) | | $X^2$ |
| **Demographics** | | | | | | | | | |
| *Age - $\bar{x}$ (SE)* | 42.7 | (0.4) | 40.2 | (0.5) | 37.3 | (0.5)* | 33.6 | (0.5)*,^ | p<0.001 |
| *Gender - % (SE)* | | | | | | | | | |
| Male | 48.3 | (0.6) | 51.5 | (0.7) | 49.5 | (1.2) | 60.5 | (1.3)*,^ | p<0.001 |
| Female | 51.7 | (0.6) | 48.5 | (0.7) | 50.5 | (1.2) | 39.5 | (1.3)*,^ | |
| *Education - % (SE)* | | | | | | | | | |
| Less than high school | 20.5 | (0.9) | 17.6 | (1.0) | 27.7 | (1.2)* | 54.4 | (1.9)*,^ | |
| High school graduate | 34.9 | (0.8) | 35.1 | (0.9) | 38.2 | (1.4) | 25.7 | (1.2)*,^ | p<0.001 |
| Some college/college graduate | 44.6 | (1.2) | 47.3 | (1.4) | 34.1 | (1.7)* | 19.9 | (1.5)*,^ | |
| **Family History of Diabetes - *% (SE)*** | | | | | | | | | |
| Yes | 22.9 | (0.7) | 21.7 | (0.8) | 29.1 | (1.0)* | 31.0 | (1.0)* | p<0.001 |
| No | 77.1 | (0.7) | 78.3 | (0.8) | 70.9 | (1.0)* | 69.0 | (1.0)* | |
| **Metabolic Markers** | | | | | | | | | |
| *Body Mass Index (kg/m$^2$) - $\bar{x}$ (SE)* | 26.5 | (0.1) | 25.3 | (0.1) | 26.6 | (0.1)* | 26.6 | (0.1)* | p<0.001 |
| *Glycemic Status - % (SE)* | | | | | | | | | |
| Diabetes (A1c ≥ 6.5%) | 4.4 | (0.3) | 3.8 | (0.3) | 8.1 | (0.5)* | 6.1 | (0.4)*,^ | |
| Pre-diabetes (A1c 5.7-6.5%) | 13.2 | (0.8) | 11.3 | (0.9) | 27.7 | (1.0)* | 16.0 | (1.1)*,^ | p<0.001 |
| Euglycemic (A1c < 5.7%) | 82.4 | (0.9) | 84.9 | (1.0) | 64.2 | (1.1)* | 77.9 | (1.2)*,^ | |
| **Health Behaviors** | | | | | | | | | |
| *Healthy Eating Index (0-100) - $\bar{x}$ (SE)* | 63.2 | (0.3) | 63.5 | (0.5) | 58.8 | (0.5)* | 64.0 | (0.5)^ | p<0.001 |
| *Smoking Status - % (SE)* | | | | | | | | | |
| Current smoker | 39.7 | (0.9) | 38.6 | (1.1) | 43.6 | (1.2)* | 50.9 | (1.0)*,^ | |
| Former | 27.9 | (0.7) | 29.3 | (0.8) | 18.2 | (1.0)* | 23.0 | (0.8)*,^ | p<0.001 |
| Non-smoker | 32.4 | (1.2) | 32.1 | (1.2) | 38.2 | (1.2)* | 26.1 | (1.1)*,^ | |
| *Alcohol consumption - % (SE)* | | | | | | | | | |
| Drinker (≥12 dks/yr) | 35.9 | (1.3) | 34.7 | (1.5) | 42.8 | (1.2)* | 37.5 | (0.9)^ | p<0.001 |
| Non-drinker (<12 dks/yr) | 64.1 | (1.3) | 65.0 | (1.5) | 57.2 | (1.2)* | 62.5 | (0.9)^ | |
| **Physical Activity** | | | | | | | | | |
| *Physical Activity Score – median (IQR)* | 12.3 | (3.5-28.9) | 13.3 | (3.7-29.6) | 9.0 | (1.4-26.0)* | 5.4 | (0.3-21.1)*,^ | p<0.001 |
| *Physical Activity Guideline Index - % (SE)* | | | | | | | | | |
| Inactive[a] | 11.9 | (0.7) | 10.2 | (0.7) | 18.7 | (1.0)* | 24.5 | (1.4)*,^ | |
| Insufficiently Active (PAS ≥0-<10) | 44.4 | (1.1) | 44.3 | (1.2) | 45.5 | (1.1) | 44.5 | (1.6) | p<0.001 |
| Active (PAS ≥10) | 43.7 | (1.3) | 45.5 | (1.5) | 35.8 | (1.4)* | 31.0 | (1.3)* | |

SE = Standard Error; PAS: Physical Activity Score; A1c: glycosylated hemoglobin; dks: drinks; yr: year; IQR: Interquartile Range. NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American.

[a]Zero activity reported.

[b]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as weighted percentage (SE).

*significantly different (p<0.05) from NHW; ^significantly different (p<0.05) from NHB.

Table 4.2. Diabetes-related mortality rates by race-ethnic group: NHANES III

| RACE-ETHNICITY | N | Death events | Baseline* $\bar{x}$ age (SE) | $\bar{x}$ age of death (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-standardized mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 4563 | 127 | 62.1 (0.8) | 75.1 (1.2) | 81,008.3 | 15.7 | 12.3 |
| **Non-Hispanic Black** | 3057 | 88 | 58.0 (1.0) | 69.7 (1.0) | 54,841.5 | 16.0 | 18.1 |
| **Mexican American** | 3097 | 116 | 54.6 (1.3) | 68.3 (1.3) | 58,086.1 | 19.9 | 26.6 |

*When examined at the Mobile Examination Center

Table 4.3. Diabetes-related mortality risk and the Physical Activity Guideline Index: NHANES III (N=10,717)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Model 1 | Model 2# | Model 3^ |
| **Physical Activity** | | | |
| *Physical Activity Guideline Index* | | | |
| Inactive | 1.00 | 1.00 | 1.00 |
| Insufficiently Active (PAS ≥0-<10) | 0.34 (0.25-0.48)* | 0.46 (0.31-0.67)* | 0.54 (0.34-0.86)* |
| Active (PAS ≥10) | 0.29 (0.20-0.42)* | 0.35 (0.23-0.53)* | 0.58 (0.36-0.94)* |
| **Demographics** | | | |
| *Age (years)* | | 1.11 (1.09-1.12)* | 1.10 (1.08-1.12)* |
| *Race-ethnicity* | | | |
| NHW | | 1.00 | 1.00 |
| NHB | | 1.42 (0.97-2.07) | 0.76 (0.53-1.09) |
| MA | | 1.61 (1.13-2.32)* | 1.00 (0.67-1.52) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.80 (0.52-1.24) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 1.05 (0.70-1.56) |
| Some college/college graduate | | | 0.74 (0.40-1.35) |
| **Family History of Diabetes** | | | |
| Yes | | | 1.00 |
| No | | | 0.77 (0.55-1.08) |
| **Metabolic Markers** | | | |
| *Body Mass Index (kg/m$^2$)* | | | 1.05 (0.99-1.08) |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.17 (0.10-0.26)* |
| Euglycemic (A1c < 5.7%) | | | 0.07 (0.04-0.12)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index (0-100)* | | | 1.00 (0.99-1.02) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.42 (0.29-1.62) |
| Non-smoker | | | 0.43 (0.28-0.66)* |
| *Alcohol consumption* | | | |
| Drinker (≥12 dks/yr) | | | 1.00 |
| Non-drinker (<12 dks/yr) | | | 0.72 (0.49-1.08) |
| **P-for-interaction** | | | |
| Race-ethnicity x PAGI | | 0.44 | 0.83 |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American. *p<0.05
#Adjusted for physical activity, age and race-ethnicity
^Adjusted for physical activity, age, race-ethnicity, gender, education, family history of diabetes, body mass index, glycemic status, healthy eating index, smoking status, and alcohol consumption

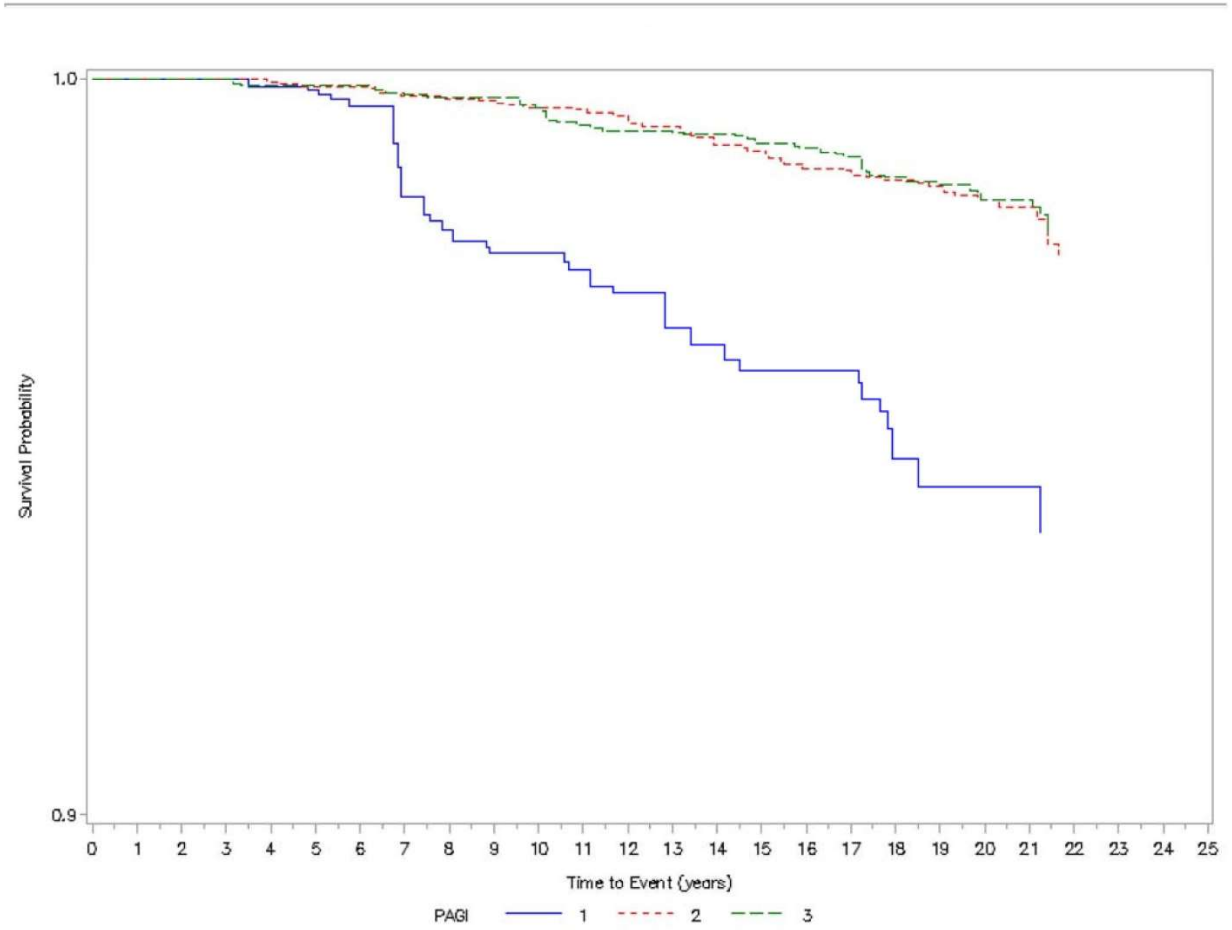


Figure 4.1. Non-Hispanic White Kaplan-Meier Survival Curve: Physical Activity Guideline Index (PAGI) and diabetes-realted mortality

PAGI 1: Inactive; PAGI 2: Insufficiently Active; PAGI 3: Active

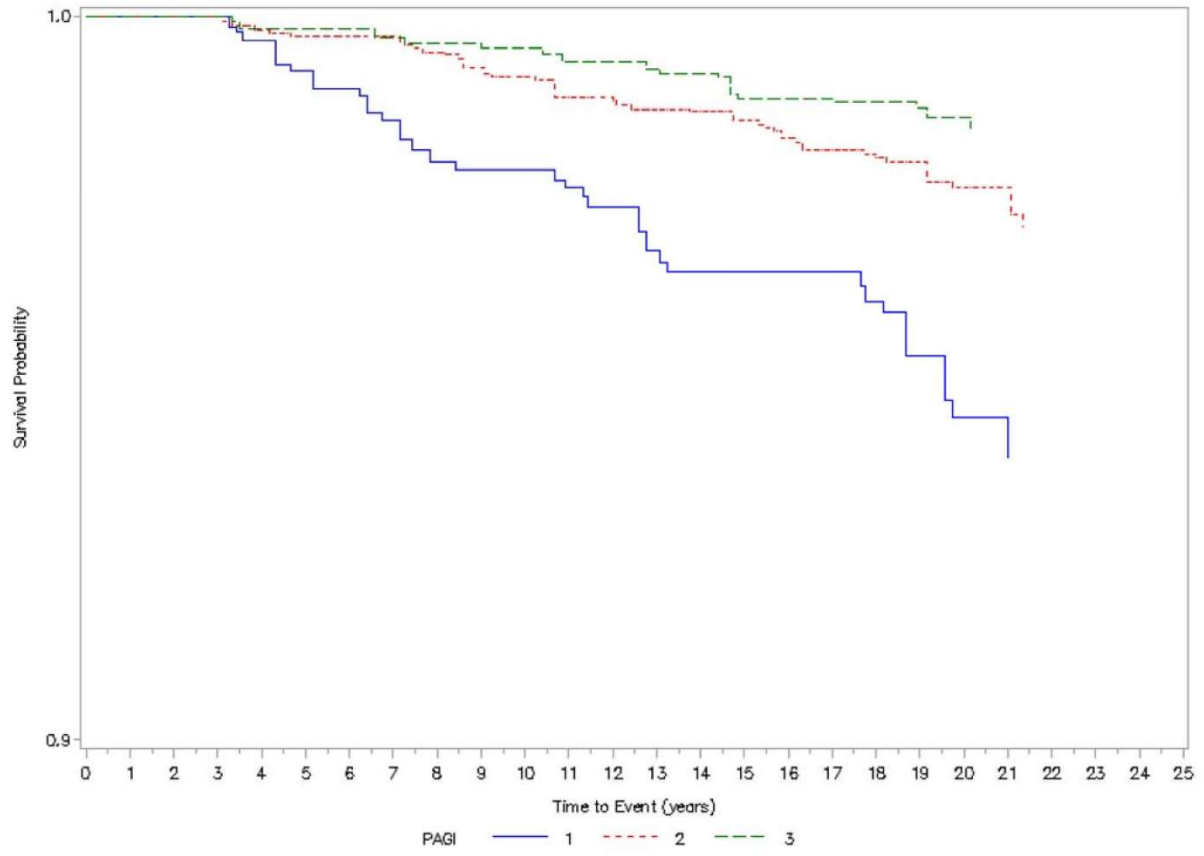


Figure 4.2. Non-Hispanic Black Kaplan-Meier Survival Curve: PAGI and diabetes-realted mortality

PAGI 1: Inactive; PAGI 2: Insufficiently Active; PAGI 3: Active

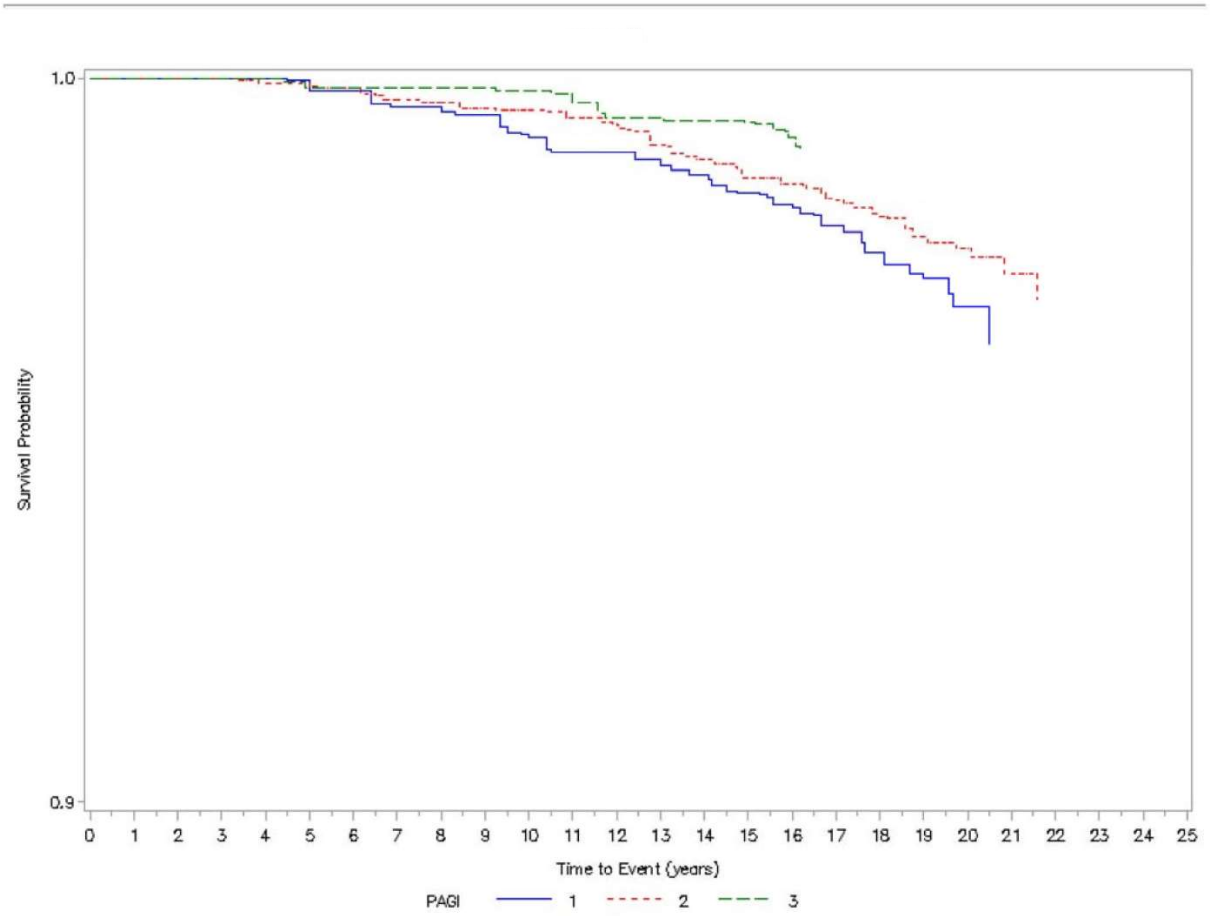


Figure 4.3. Mexican American Kaplan-Meier Survival Curve: PAGI and diabetes-realted mortality

PAGI 1: Inactive; PAGI 2: Insufficiently Active; PAGI 3: Active

Table 4.4. Diabetes-related mortality risk and the Physical Activity Guideline Index stratified by race-ethnicity: NHANES III

| | Physical Activity Guideline Index | | | |
|---|---|---|---|---|
| | Inactive | Insufficiently Active | Active | p-for-trend |
| **Physical Activity Score** | 0 | >0-<10 | ≥10 | |
| **Total** | | | | |
| N | 1946 | 4829 | 3942 | |
| No. of deaths | 102 | 151 | 78 | |
| Person-years | 33527.8 | 88132.0 | 72276.1 | |
| Unadjusted HR | 1.00 | 0.34 (0.25-0.48)* | 0.29 (0.20-0.42)* | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.54 (0.34-0.86)* | 0.58 (0.36-0.94)* | p=0.08 |
| **Non-Hispanic White** | | | | |
| N | 552 | 1991 | 2020 | |
| No. of deaths | 32 | 50 | 45 | |
| Person-years | 8837.8 | 35847.4 | 36323.1 | |
| Unadjusted HR | 1.00 | 0.30 (0.18-0.48)* | 0.26 (0.16-0.43)* | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.51 (0.29-0.89)* | 0.57 (0.33-1.00)^ | p=0.14 |
| **Non-Hispanic Black** | | | | |
| N | 590 | 1432 | 1035 | |
| No. of deaths | 32 | 40 | 16 | |
| Person-years | 997.2 | 25706.1 | 19218.3 | |
| Unadjusted HR | 1.00 | 0.44 (0.26-0.75)* | 0.27 (0.12-0.58)* | p=0.002 |
| Adjusted HR[a] | 1.00 | 0.62 (0.34-1.15) | 0.56 (0.27-1.19) | p=0.14 |
| **Mexican American** | | | | |
| N | 804 | 1406 | 887 | |
| No. of deaths | 38 | 61 | 17 | |
| Person-years | 14712.8 | 26638.5 | 16734.8 | |
| Unadjusted HR | 1.00 | 0.76 (0.52-1.12) | 0.32 (0.17-0.60)* | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.84 (0.59-1.19) | 0.50 (0.23-1.09) | p=0.04 |

[a]Adjusted for: age, gender, education, family history of diabetes, body mass index, glycemic status, healthy eating index, smoking status, alcohol consumption. HR: Hazard Ratio. *p<0.05. ^p=0.048

**Discussion**

The current study is the first to examine the potential effect modification of race-ethnicity on the relationship between aerobic PA and diabetes-related mortality. In the non-stratified analysis, the results indicate that accumulation of any volume of PA is sufficient to reduce risk for diabetes-related mortality. Furthermore, no significant trend was evident. In the race-ethnicity specific analysis, the results allude to possible effect modification by race-ethnicity in that only NHW had a statistically significant reduction in risk for diabetes-related mortality whether insufficiently active or active. Moreover, a significant dose-response was found only for MA 9illusrtaed by the significant p-for-trend). However, there was no statistically significant interaction between race-ethnicity and PA in the age-adjusted or fully-adjusted analyses which suggests no effect modification.

The results of the current study found no significant trends in the fully adjusted analyses for either NHW or NHB suggesting that any volume of activity may be sufficient to reduce diabetes-related mortality risk and accruing more activity does not lead to more favorable risk reductions. The magnitude of the hazard ratio estimates were similar between NHW and NHB, especially in those who were active. However, the results also indicate that in the fully adjusted models, the risk reductions among insufficiently active and active NHB were not statistically significant. It is important to note that the total number of deaths as well as the sample size was lower among insufficiently active and active NHB compared to NHW. These factors could have very well influenced the results as the lack of power could have driven the large confidence intervals, thus the lack of statistical significance. Given that previous analyses (99-103) examining effect modification by race-ethnicity on PA and all-cause mortality have consistently shown no differences between NHB and NHW, it is possible that no effect modification exists between NHW and NHB for PA and diabetes-related mortality. It is hypothesized that given

additional time for follow-up in the NHANES III cohort, the magnitude of mortality events among NHB will increase allowing for more precise estimates of risk and, potentially, attainment of statistical significance for the PA and race-ethnicity interaction.

MA were the only race-ethnic group to present statistical evidence for a dose-response relationship (evidenced by a statistically significant p-for-trend) associated with PA and diabetes-related mortality. Furthermore, MA were the only group who had no statistically significant reduction in the insufficiently active group in the unadjusted analysis; indicating a potential difference in the minimum volume of PA needed to reduce risk for diabetes-related mortality when compared to NHW and NHB. Despite attempting to adjust for confounders, it is possible other variables play a role in mediating the effect of PA on diabetes-related mortality including occupational PA (OPA), increased allostatic load (30, 104), and issues related to diminished access to healthcare (103, 105). Further research is warranted specifically in those identifying as MA to further quantify the dose-response relationship between LTPA and diabetes-related mortality. More specifically, examination of potential physiological mechanisms that may explain the current findings as well as the potential interaction between PA other measures, such as allostatic load, is needed within the scope of race-ethnicity and diabetes-related mortality.

There are several strengths to the current study. First, the large, population-based sample allows for a generalization of the results to the population of the U.S. Second, the methodology behind the NDI mortality linkage has been previously validated (72, 106). Third, this is the first study to examine the possible effect modification of race-ethnicity on the relationship between PA and diabetes-related mortality. Only two previous studies have investigated this relationship (11, 12), both of which found an inverse relationship between PA and diabetes-related mortality

risk. However, both studies failed to examine effect modification by race-ethnicity. This study also adds to the two previous studies (10, 62) that have examined the effect modification of race-ethnicity on aspects of the diabetes life experience. Briefly, a meta-analysis by Boyer et al. (10) found effect modification by race-ethnicity on the relationship between PA and type 2 diabetes risk. Specifically, when comparing the most active to least active, NHB and Hispanics had no significant reduction in risk for type 2 diabetes. An analysis by Glenn et al. (62) found similar risk reductions for all-cause mortality across quartiles of PA in NHW and NHB. Finally, this study also addresses the recommendations outlined by the 2008 Physical Activity Guidelines Committee report (33) which state that there is a need to examine the interaction between race-ethnicity and PA on a number of health-related outcomes including mortality. It is evident that more research is needed to fully understand how PA may be associated with differential diabetes-related mortality across race-ethnic groups.

This study is not without limitations. The first is the inability to track potential changes in PA measures over the course of follow-up. Moreover, there is always the possibility of residual confounding, particularly from constructs such as allostatic load, markers of socioeconomic status not included in this analysis, and diabetes medication use. A second limitation is that duration of PA bouts was not measured as part of the NHANES III PA interview. Thus, a true measure of total LTPA volume was unable to be quantified. Furthermore, due to the nature of self-report data, the PA data is subject to both recall bias as well as the social desirability effect. Next, previous studies have shown low sensitivity and specificity in how diabetes is classified as a cause/contributing cause of death (32). Thus, the under-reporting of deaths attributable to diabetes could be a factor in the overall large confidence intervals and HR estimates across categories of the PAGI. A final limitation is that the public-use mortality data file limits the

ability to examine mortality specific to diabetes "type". While the vast majority of diabetes deaths are related to type 2 diabetes (1), some deaths may have come from type 1 or others (excluding gestational diabetes). Thus, a sensitivity analysis isolating death from type 2 diabetes is warranted in future research.

In conclusion, the results of this study indicate that accumulation of any volume of PA is associated with a significantly lowered risk for diabetes-related mortality. In the race-ethnicity specific analyses, estimates for the reduction in risk among NHW and NHB were similar in magnitude and additionally suggested that any volume of PA is associated with a significantly lowered risk for diabetes-related mortality; although there was no attainment of statistical significance in NHB. Moreover, there was evidence of a dose-response relationship only among MA illustrated by the significant trend. Nevertheless, no statistical significance was achieved across any level of the PAGI for MA. These results allude to potential effect modification by race-ethnicity in that NHW were the only group that had a statistically significant reduction in risk for diabetes-related mortality across categories of the PAGI. However, there was no statistically significant interaction between race-ethnicity and PA. Thus, the results advocate that until more data are available within the NHANES III cohort, there is an inability to truly determine, statistically, the extent in which effect modification does or does not exist across race-ethnicity.

Future studies should investigate these relationships using more robust measures of PA; either more detailed questionnaires including duration or via objective monitors such as accelerometers. The continuous NHANES has a more robust PA interview questionnaire (1999-2004) that includes duration of PA, as well as accelerometer-derived PA measures (2003-2006), and could be used to further study the effect modification of race-ethnicity on the relationship

between PA and diabetes-related mortality. As stated before, with the continued follow-up time of the NHANES III cohort and as more data becomes available from the NDI, the ability to estimate more accurate risk reductions will become plausible.

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# APPENDICIES

## Appendix 1: National Death Index causes of death tables

The following tables provide a visual representation of the International Statistical Classification of Diseases, Injuries, and Causes of Death codes used to (a) classify death from diabetes mellitus (Table A1.1) and (b) provide a frame of reference for the recoding of all deaths to match the ICD-10 code for cause of death (Table A1.2)

The following tables provide a visual representation of the International Statistical Classification of Diseases, Injuries, and Causes of Death codes used to (a) classify death from diabetes mellitus (Table 1) and (b) define the ICD-10 codes used to categorize diabetes mortality (Table 2)

Table A1.1. Mortality codes used to classify death from type 2 diabetes

| UCOD_LEADING RECODE | 113 Recode | Cause Title and ICD-10 Codes |
|---|---|---|
| 007 | 046 | Diabetes mellitus (E10-E14) |

*Adapted from Appendix 4. Tenth Revision 113 Selected Causes of Death (UCOD_113) (1)

Table A1.2. ICD-10 codes

| ICD-10 Code | Cause description |
|---|---|
| E10 | Insulin-dependent diabetes mellitus |
| E11 | Non-insulin-dependent diabetes mellitus |
| E12 | Malnutrition-related diabetes mellitus |
| E13 | Other specified diabetes mellitus |
| E14 | Unspecified diabetes mellitus |

*Adapted from LIST OF ALL VALID ICD-10 CODES, 1999-2011

Table 2: Modified version of the “List of all valid ICD-10 codes, 1999-2011” illustrating the cause descriptions associated with death from diabetes mellitus

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## Appendix 2

## The protective role of physical activity on type 2 diabetes: an analysis of effect modification by race-ethnicity

**Protective role of physical activity on type 2 diabetes: Analysis of effect modification by race–ethnicity**

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**Abstract**

**Background:** It is well known physical activity (PA) plays a role in the prevention of type 2 diabetes (T2D). However, the extent to which PA may impact T2D risk among different race-ethnic groups is unknown. Therefore, the purpose of this study was to systematically examine the effect modification of race-ethnicity on PA and T2D. **Methods:** PubMed and Embase databases were systematically searched through June 2016. Study assessment for inclusion was conducted in three phases: 1) title review (N= 13,022), 2) abstract review (N=2,200), and 3) full text review (N=265). A total of 27 studies met the inclusion criteria and were used in the analysis. Relative risks (RRs) and 95% confidence intervals (CIs) were extracted and analyzed using the Comprehensive Meta-Analysis software. All analyses used a random-effects model. **Results:** A significant protective summary RR, comparing the most active group to the least active PA group, was found for non-Hispanic White (RR 0.71, 95% CI 0.60-0.85), Asians (RR 0.76, 95% CI 0.67-0.85), Hispanics (RR 0.75, 95% CI 0.64-0.89), and American Indians (RR 0.73, 95% CI 0.60-0.88). The summary effect for non-Hispanic Blacks (RR 0.91, 95% CI 0.76-1.08) was non-significant. **Conclusions:** The results of this study indicate that PA (comparing most to least active groups) provides significant protection from T2D with the exception of non-Hispanic Blacks. The results also indicate a need for race-ethnicity specific reporting of RRs in prospective cohort studies that incorporate multi-ethnic samples.

**Highlights:** There is a significant and similar risk reduction associated with physical activity across race-ethnicity with the exception of non-Hispanic blacks

There are several physiological mechanisms that may explain this finding that are in need of further exploration in the context of physical activity

**Keywords:** Race, ethnicity, diabetes, risk, physical activity

## INTRODUCTION

The prevalence of type 2 diabetes among adults in the United States (U.S.) is estimated to be anywhere from 9.3-14.5%, depending upon the dataset and diagnostic criteria (1, 2). Furthermore, by the year 2050, the type 2 diabetes prevalence in the U.S. is projected to reach upwards of 21-33% (3). However, substantial race-ethnic disparities exist in the prevalence of type 2 diabetes. At 15.9%, American Indian/Alaskan Natives have the highest estimated prevalence of type 2 diabetes (1). The next highest prevalence rates are found among Non-Hispanic Blacks (NHB, 13.2%), Hispanics (12.8%), Asians (9.0%) and those who are non-Hispanic White (NHW, 7.6%) (1). Race-ethnic disparities in the prevalence of type 2 diabetes are expected to persist4: the projected 50 year increase in prevalence of type 2 diabetes will be highest among NHBs, followed by Hispanics and other ethnicities compared to NHW.

Physical activity (PA) is an important component of type 2 diabetes prevention initiatives5 and has been shown to reduce the risk of type 2 diabetes (6). However, the extent of type 2 diabetes protection associated with PA has yet to be fully examined in regards to effect modification by race-ethnicity. A narrative review by Gill et al. (7) suggested varying thresholds of PA protection against type 2 diabetes may across race-ethnic groups. Moreover, the authors also suggested that the current U.S. Department of Health and Human Services (DHHS) uniform guideline of 150 min moderate-intensity aerobic PA per wk 8 may not provide equal protection against developing type 2 diabetes across race-ethnic groups.

The 2008 Physical Activity Guidelines Committee Report (9), indicates significant need to further understand the effects of PA on diabetes risk among ethnically-diverse populations. While meta-analyses have examined and established a clear inverse relationship between PA and

type 2 diabetes risk (6, 10), to our knowledge, no meta-analysis has assessed effect modification of this relationship by race-ethnicity. Therefore, the purpose of this systematic review and meta-analysis was to compile the evidence from prospective cohort studies on potential effect modification of the aerobic PA and type 2 diabetes risk relationship by race-ethnic groups.

## METHODS

### Data sources and searches

Systematic searches of the literature were independently conducted in PubMed and Embase by two authors (W.R.B. and E.C.F.). A modified version of the search criteria employed by Aune et al. (6) was used: (physical activity OR exercise OR sports OR walking OR biking OR running OR fitness OR exercise test OR inactivity OR sedentary activity) AND diabetes AND (case–control OR retrospective OR cohort OR cohorts OR prospective OR longitudinal OR follow-up OR cross-sectional OR trial) AND (ethnic OR ethnic group OR race OR racial group). Furthermore studies included in another meta-analysis we screened as well (6). Standard guidelines for conducting and reporting meta-analyses were followed (11).

### Study Selection

Research articles were examined for the following eligibility criteria: human participants who were without type 2 diabetes at the start of the studies and were adults (≥18 years) at the time of follow-up; assessed aerobic-based PA; published or available in English; were prospective cohort studies; assessed and reported the race-ethnicity specific relative risks (RR) for type 2 diabetes; adjusted risk estimates for age; and allowed for the determination of a most versus least physically active group. The article screening process is presented in Figure A1.1. A

total of 27 individual articles met the full eligibility criteria (12-38). Race-ethnic groups identified and used in the analyses were NHW, NHB, Asian, Hispanic, and American Indian.

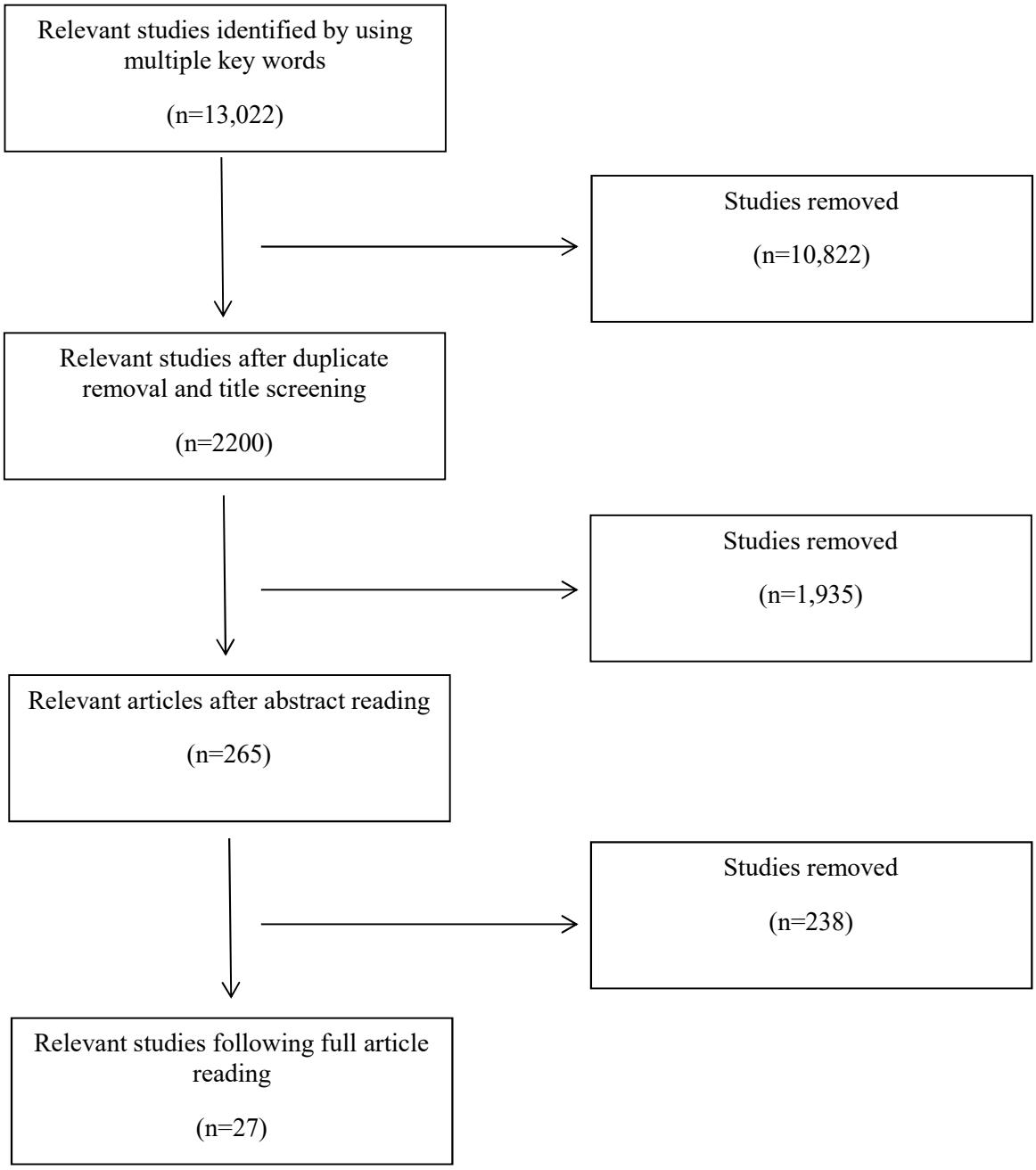


Figure A1.1. PRISMA Flow Chart

**Data Extraction and Quality Assessment**

Relative risks and 95% confidence intervals (CIs) for diabetes were extracted and entered into Comprehensive Meta-Analysis (CMA) software version 3.0 (Biostat, Englewood, NJ, USA, 2014). Random-effects models were used for all analyses, given that true effects are likely to vary across studies (rather than a fixed-model, which assumes the same value or true effect for all studies) (39). In all studies, the RR estimates extracted were those comparing the highest to the lowest level of PA. A second analysis was conducted among studies (17, 21, 28, 37, 38) that used the current DHHS moderate-intensity aerobic PA guideline of at least 150 min/wk as their demarcation point for PA (8) (i.e., comparing those who met the recommendations to those who did not). Race-ethnic groups utilized in the secondary analysis included all identified previously except American Indians.

Quality assessment was performed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (40) which uses a 14 question scale (higher score corresponding to higher quality) to assess quality. All studies were independently rated by two researchers (W.B. and E.F.); all studies were rated as 'good' (average Quality Assessment score= 10.9, range 10-11). Since the studies were all of good quality, analyses examining the potential impact of differential study quality on the main RR effects were not conducted.

**Data Synthesis and Analysis**

Data analysis was conducted using CMA software version 3.0. Heterogeneity was quantified using $I^2$; a descriptive index that estimates the ratio of true variation (heterogeneity) to total variation across the observed effect sizes (39). An overall main effect of PA on type 2 diabetes was calculated for each race-ethnic group. A second analysis was conducted to assess

the overall effect of meeting the 2008 DHHS moderate-intensity aerobic PA recommendation on type 2 diabetes risk (8). Significance for the main effects was set at 0.05. Potential publication bias was examined using a funnel plot.

**RESULTS**

A total of 1,150,574 participants were identified across all studies meeting the inclusion criteria. Table A2.1 illustrates the characteristics of the individual studies (N=27). Duration of follow-up ranged from two (30) to twenty-eight years (35). Studies were conducted in the U.S. (n=9) and internationally (n=17), with one study conducted in both the U.S. and Canada (30). The method for identifying cases of type 2 diabetes varied by study and included ascertainment by medical records; report of insulin or medication use; 2 hr oral glucose tolerance tests; fasting plasma glucose, or self-report of a physician diagnosis. Potential publication bias was not detected in the funnel plot (supplemental figure 1 [supp. 1.]).

Figures 2-6 show the results comparing the most active to the least active groups among the race-ethnic groups examined (Figure 2: NHW, Figure 3: Asian, Figure 4: Hispanic, Figure 5: American Indian, Figure 6: NHB). Significant, and similar, summary RRs for PA and type 2 diabetes were found for NHWs (RR 0.71, 95% CI 0.60-0.85), Asians (RR 0.76, 95% CI 0.67-0.85), Hispanics (RR 0.74, 95% CI 0.64-0.84), and American Indians (RR 0.73, 95% CI 0.60-0.88). The summary effect for NHBs (RR 0.91, 95% CI 0.76-1.08) did not attain statistical significance.

In analyses examining the 2008 DHHS moderate-intensity aerobic PA recommendation and diabetes risk by race-ethnicity (data not shown), a suggestion of a significant trend was observed for NHWs (RR 0.75. 95% CI 0.55-1.01, p=0.06) and Asians (RR 0.80, 95% CI 0.64-1.01, p=0.06), but the estimates did not attain statistical significance. The summary effects for

meeting the 2008 DHHS moderate-intensity aerobic PA recommendation and diabetes risk among NHBs (RR 1.26, 95% CI 0.84-1.90) and Hispanics (RR 0.95, 95% CI 0.66-1.65) did not attain statistical significance.

Sensitivity analyses were conducted to examine the effect of removing a single study on the overall summary effects by race-ethnic group (data not shown). No significant changes were found to the race-ethnic specific summary RRs with the exception of Hispanics. When removing Hsia et al. (18) from the Hispanic analysis, statistical significance was lost (RR 0.79, 95% CI 0.60-1.03, p=0.09). Furthermore, when removing Ma et al. (25) from the analysis, similar results were found (RR 0.89, 95% CI 0.65-1.22, p=0.46).

Table A2.1. Study characteristics

| Author, year | Race-Ethnicity | Country | Gender | Age (years) | N | Physical activity measure | Follow-up (years) | Adjustments |
|---|---|---|---|---|---|---|---|---|
| **Burchfield, 1995** | Asian | U.S. | M | 45 - 68 | 6,815 | hrs x estimated $O_2$ consumption | 6 | age, BMI, subscapular/triceps skinfold ratio, systolic blood pressure, triglycerides, glucose, hematocrit, parental history of diabetes |
| **Burke, 2007** | NHW | Australia | M/F | 15 - 88 | 514 | d/wk | 14 | sex, age, BMI, location |
| **Fan, 2015** | Asian | China | M/F | 35 - 74 | 6,348 | MET-hrs | 7.9 | age, sex, geographic region (north or south), educational level (0–6, 7–9, or ≥10 yr), cigarette smoking (never, ever, or current), alcohol consumption (yes or no), BMI, waist circumference |
| **Fretts, 2009** | American Indians | U.S. | M/F | 45 - 74 | 1,651 | MET-hrs/wk | 10 | age, study site, sex, education (less than high school, high school, post-high school), cigarette smoking (never, ever, current), alcohol use (never, ever, current), FH of diabetes |
| **Fretts, 2014** | American Indians | U.S. | M/F | 18 - 74 | 1,639 | Steps/d | 8 | age, sex, site, education (years), FH of diabetes |
| **Honda, 2015** | Asian | Japan | M/F | 30 – 64 | 26,628 | MET-hrs | 5.2 | age, sex, shift work, sleep duration, alcohol consumption, smoking, hypertension, a family history of diabetes, occupational activity, and walking for commuting to and from work |
| **Hsia, 2005** | NHW, Asian, Non-Hispanic Black, Hispanic, American Indian | U.S. | F | No range presented | Total: 86,708 NHW: 74,240 NHB: 6,465 Asian: 2,445 Hispanic: 3,231 American Indian: 327 | MET-hrs/wk | 4 - 8 | alcohol (past/never vs current drinker), education, smoking, hypertension, hypercholesterolemia, dietary fiber (g), percent energy from carbohydrate |
| **Hu, 2004** | NHW | Finland | M/F | 45 - 64 | 4,369 | min | 9.4 | age, sex, study year, systolic blood pressure, smoking status, education, BMI |
| **James, 1998** | Non-Hispanic Black | U.S. | M/F | 30 – 55 | 916 | Categorized by min into inactive, moderate or strenuous | 5 | age, sex, education, BMI, WHR |

Table A2.1 continued

| Author, year | Race-Ethnicity | Country | Gender | Age (years) | N | Physical activity measure | Follow-up (years) | Adjustments |
|---|---|---|---|---|---|---|---|---|
| **Joseph, 2016** | NHW, Asian, Non-Hispanic Black, Hispanic | U.S. | M/F | 45 - 84 | Total: 5,348 NHW: 2,277 Non-Hispanic Black: 1,293 Asian: 676 Hispanic: 1,102 | MET-min/wk | 11.1 | age, education, sex, study site, race/ethnicity, occupational status, alcohol use, estimated glomerular filtration rate, other cardiovascular health components |
| **Koloverou, 2014** | NHW | Greece | M/F | 32 - 59 | 1,485 | Total min | 10 | age |
| **Kriska, 2003** | American Indian | U.S. | M/F | 15 - 59 | 1,728 | MET-hrs/wk | 6 | age, BMI |
| **Lee, 2012** | Asian | Korea | M | ≥18 | 675,496 | min/wk | 7.5 | age, smoking status, alcohol intake, hypertension, parental diabetes, baseline glucose, BMI |
| **Ma, 2012** | NHW, Asian, Non-Hispanic Black, Hispanic | U.S. | F | 50 - 79 | Total: 158,833 NHW: 133,541 Non-Hispanic Black: 14,618 Asian: 4,190 Hispanic: 6,484 | MET-hrs/wk | 10.4 | age, FH of diabetes, hormone therapy use, study arm, each lifestyle risk factor |
| **Nakanishi, 2004** | Asian | Japan | M | 35 - 59 | 2,924 | Daily energy expenditure (kcals) | 7 | age, FH of diabetes, alcohol consumption, cigarette smoking, BMI, weekly energy expenditure on physical exercise, systolic blood pressure, HDL cholesterol, triglycerides |
| **Okada, 2000** | Asian | Japan | M | 35 - 60 | 6,013 | d/wk | 59,966 person-years | age, BMI, alcohol consumption, smoking habits, blood pressure, parental history of Type 2 diabetes |
| **Panagiotakos, 2008** | NHW | Greece | M/F | >18 | 1,806 | MET-min/wk | 5 | age |
| **Shi, 2013** | Asian | China | M | 40 - 74 | 51,464 | METS | 5.4 | age, energy intake, smoking, alcohol consumption, education level, occupation, income FH of diabetes |
| **Tonstad, 2013 (subsample of Non-Hispanic Blacks)** | Non-Hispanic Black | U.S. and Canada | M/F | ≥30 | 7,160 | d/wk | 2 | age |
| **Tsai, 2015** | Asian | Taiwan | M/F | ≥53 | 2,995 | d/wk | 14 | age |

Table A2.1 continued

| Author, year | Race-Ethnicity | Country | Gender | Age (years) | N | Physical activity measure | Follow-up (years) | Adjustments |
|---|---|---|---|---|---|---|---|---|
| **Villegas, 2006** | Asian | China | F | 40 - 70 | 70,658 | METS | 4.6 | age, kcal/d, education level, income level, occupation, smoking, alcohol, hypertension, chronic diseases |
| **Villegas, 2009** | Asian | China | F | 40 - 70 | 62,227 | METs/d | 4.6 | age, WHR, BMI, kcal/d, alcohol consumption, smoking, education level, income level, occupation, hypertension |
| **Waki, 2005** | Asian | Japan | M/F | 40 - 59 | 28,896 | times/wk engaged in activity | 10 | age |
| **Waller, 2010** | NHW | Finland | M/F | ≥18 | 20,487 | MET-hrs/d | 28 | age, BMI |
| **Wang. 2010** | American Indians | U.S. | M/F | 45 - 74 | 1,677 | MET-hrs/wk | 7.8 | age, sex |
| **Xu, 2012** | Asian | China | M/F | ≥35 | 3,031 | min/wk | 3 | age, sex, residence area, educational attainment, BMI category, cigarette smoking, alcohol drinking, TV viewing, vegetables intake, meat intake, diagnosed hypertension |
| **Xu, 2015** | Asian | China | M/F | ≥35 | 4,550 | min/wk | 3 | age, gender, educational attainment, FH/PA, body weight status, cigarette smoking, alcohol drinking, TV viewing, vegetables intake, meat intake, diagnosed hypertension |

U.S. = United States, M = Male, F = Female, MET = Metabolic Equivalent, hr = Hour, BMI = Body Mass Index, WHR = Waist-to-hip ratio, kcal = Kilocalorie, FH = Family History, TV = Television, HDL = High-density lipoprotein cholesterol

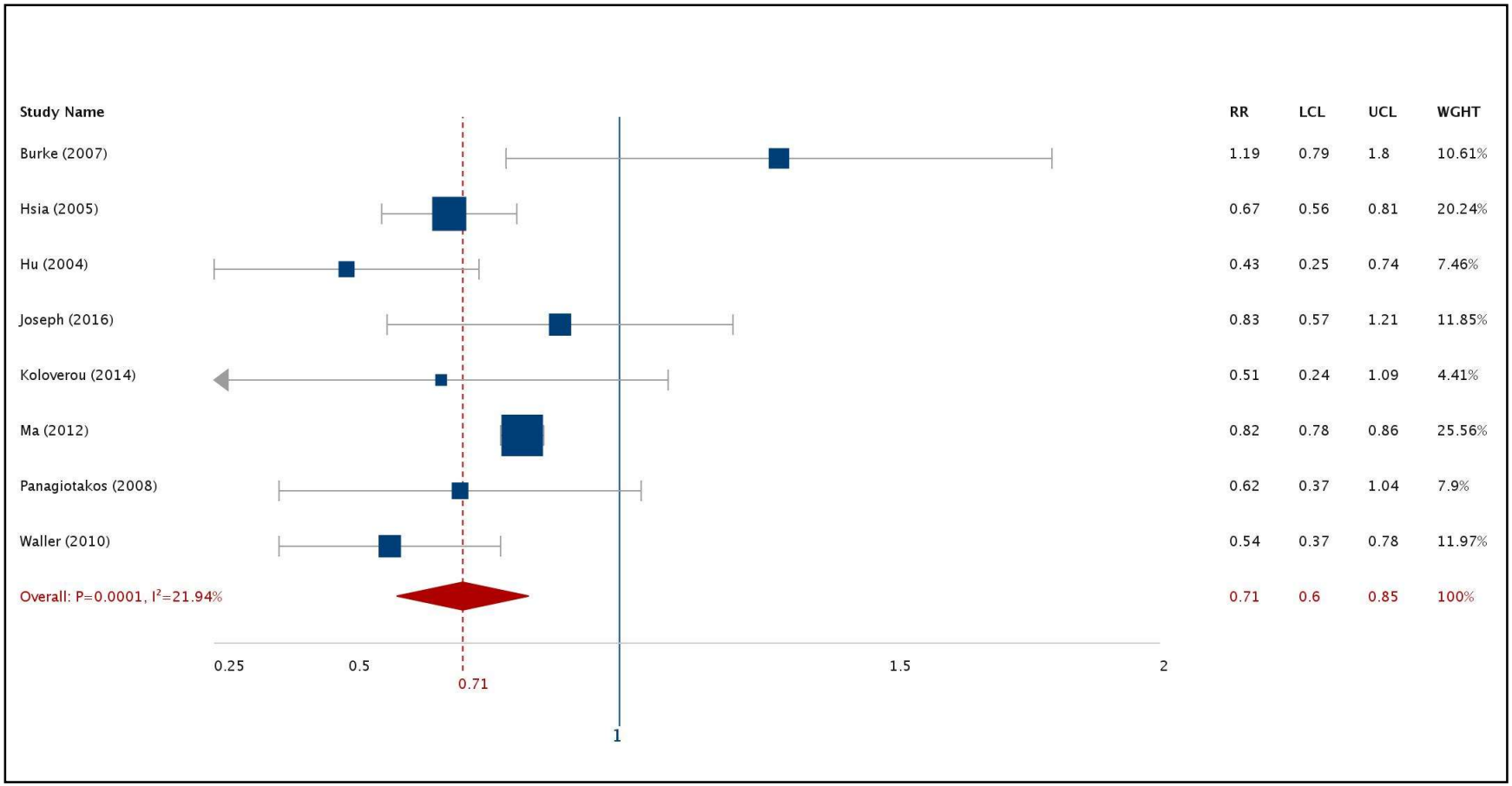


Figure A2.2. Relative risks for diabetes by aerobic physical activity (most vs. least): NHW adults.

N = 238,719. RR: Relative Risk. LCL: Low 95% Confidence Limit. UCL: Upper 95% Confidence Limit. WGHT: Weight

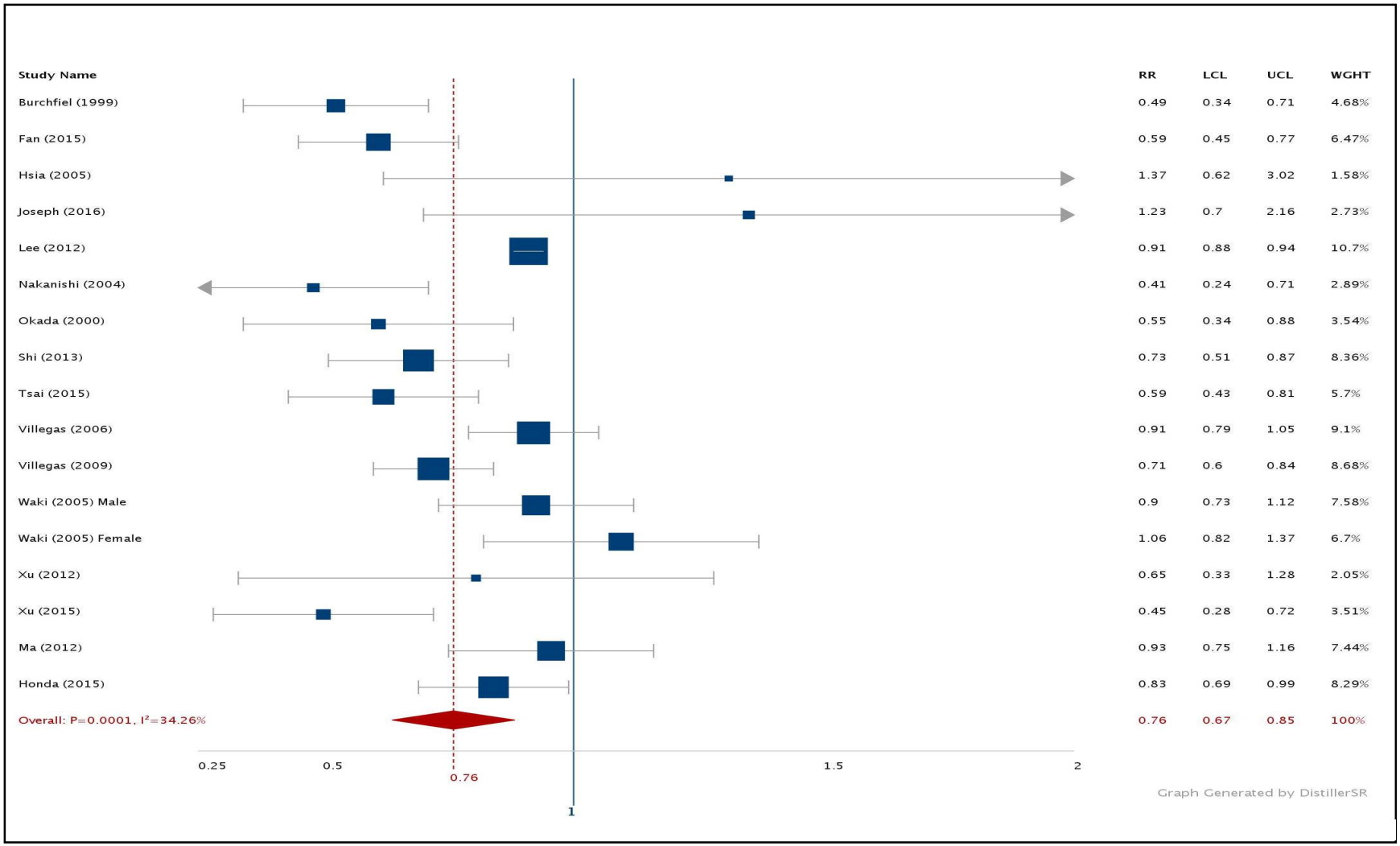


Figure A2.3. Relative risks for diabetes by aerobic physical activity (most vs. least): Asian adults.

N = 928,319. RR: Relative Risk. LCL: Low 95% Confidence Limit. UCL: Upper 95% Confidence Limit. WGHT: Weight

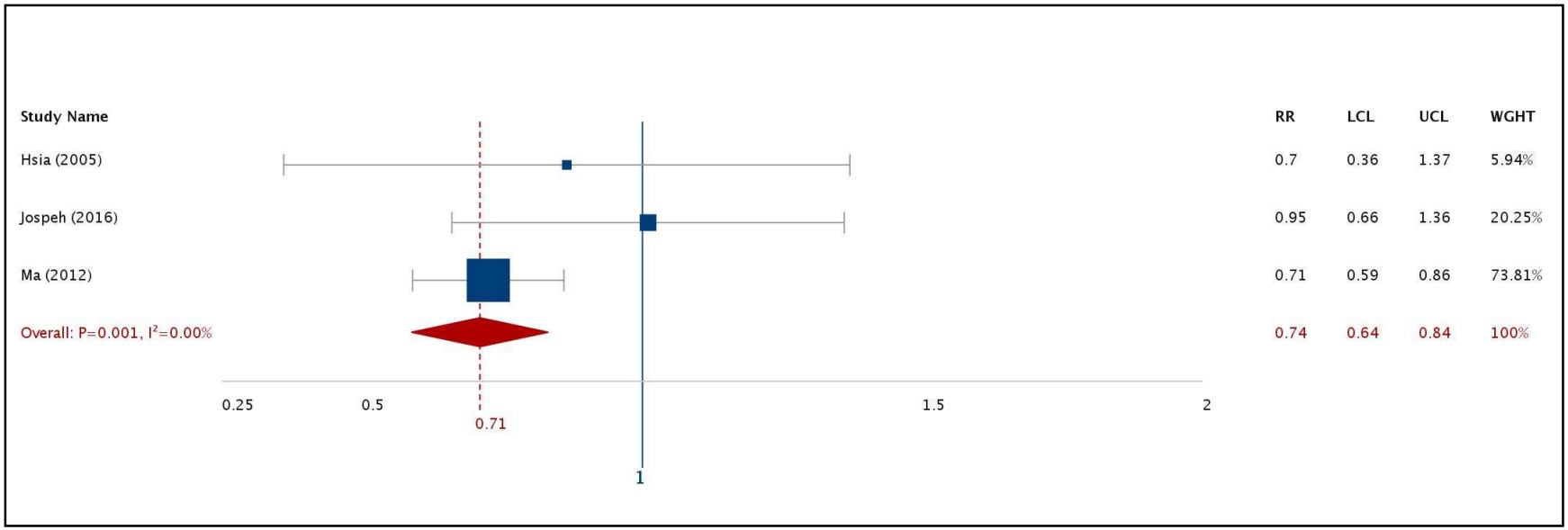


Figure A2.4. Relative risks for diabetes by aerobic physical activity (most vs. least): Hispanic adults.

N = 10,817. RR: Relative Risk. LCL: Low 95% Confidence Limit. UCL: Upper 95% Confidence Limit. WGHT: Weight

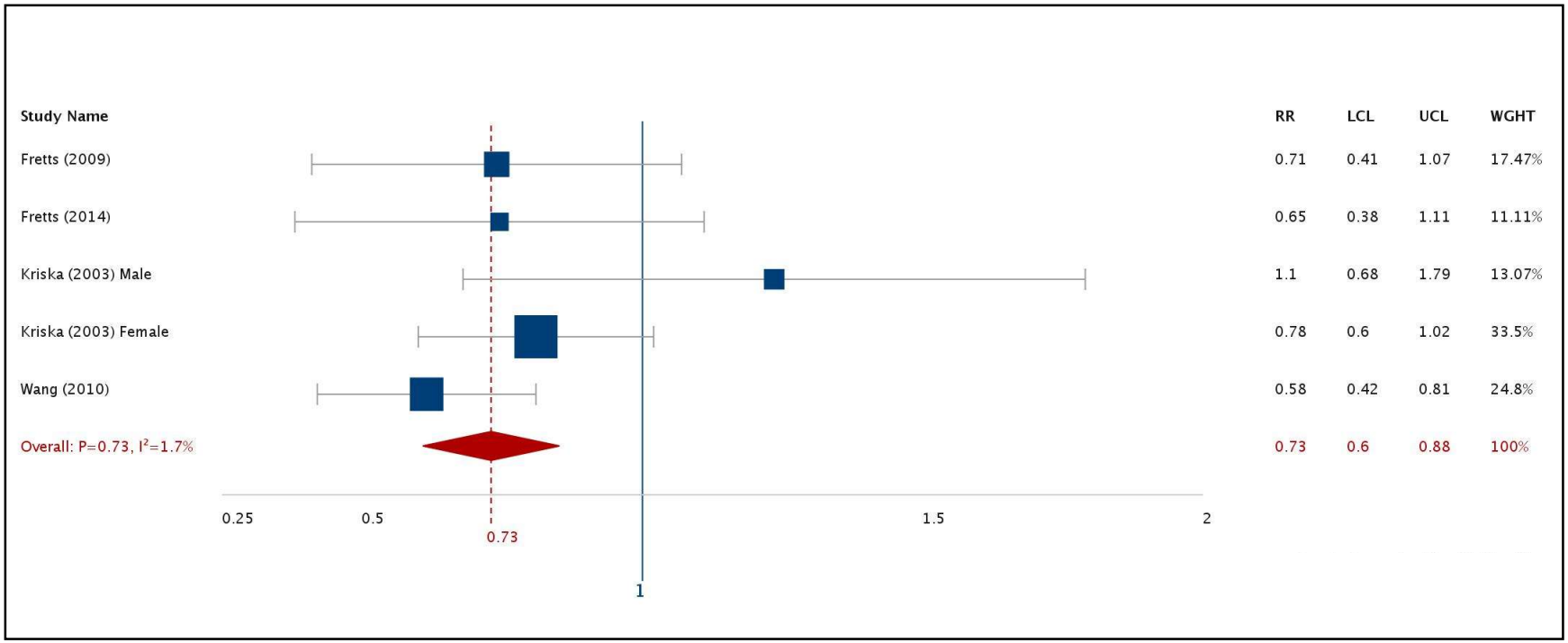


Figure A2.5. Relative risks for diabetes by aerobic physical activity (most vs. least): American Indian adults.

N = 7,022. RR: Relative Risk. LCL: Low 95% Confidence Limit. UCL: Upper 95% Confidence Limit. WGHT: Weight

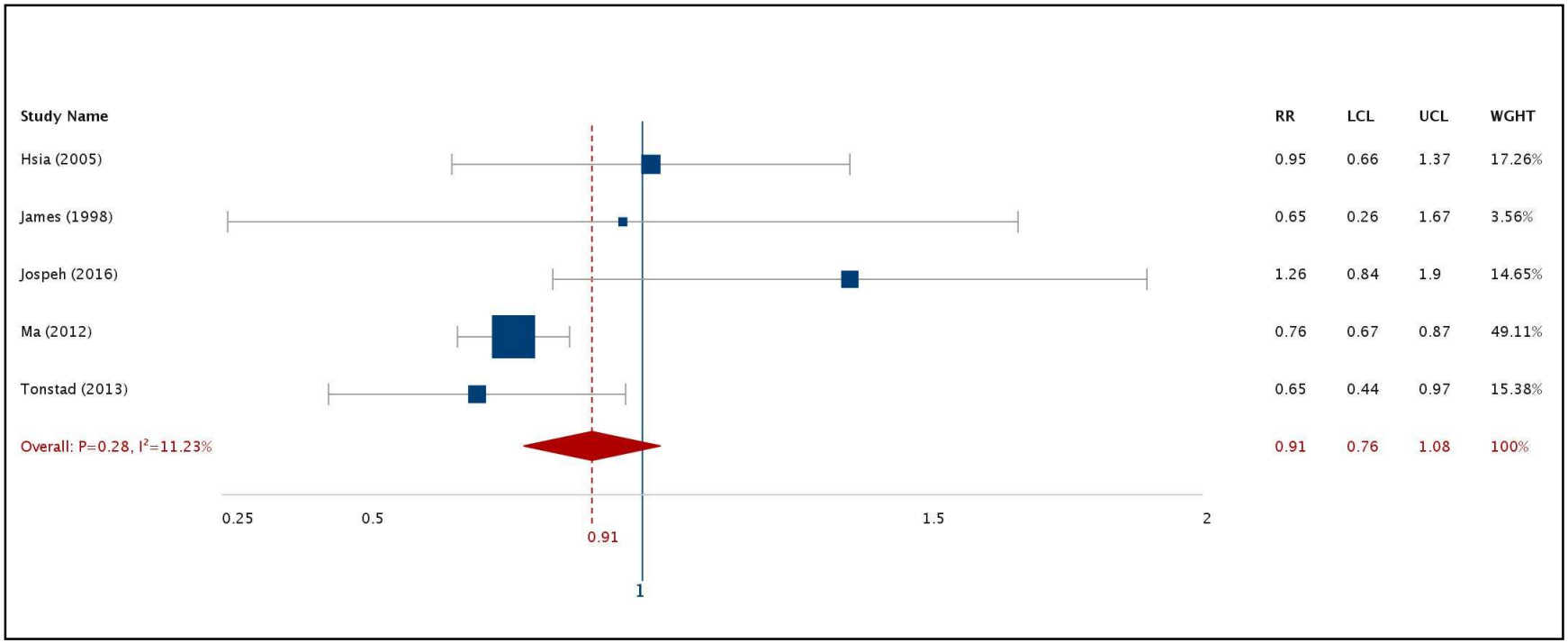


Figure A2.6. Relative risks for diabetes by aerobic physical activity (most vs. least): Non-Hispanic Black adults

N = 30,452. RR: Relative Risk. LCL: Low 95% Confidence Limit. UCL: Upper 95% Confidence Limit. WGHT: Weight

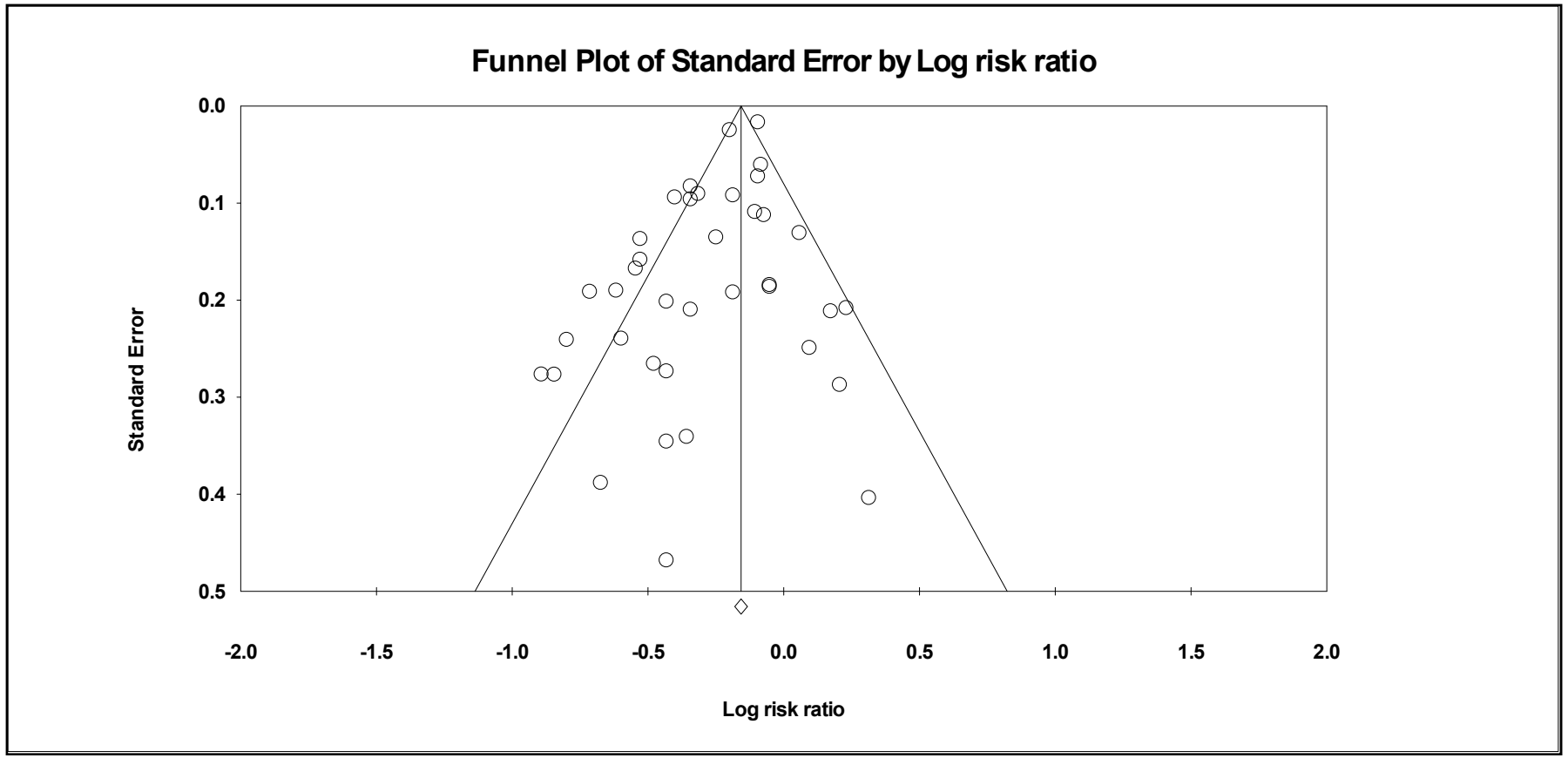


Figure A2.7. Funnel plot assessing publication bias within prospective cohort studies examining PA and type 2 diabetes risk.

## DISCUSSION

This systematic review and meta-analysis provides insight into race-ethnic differences in the effect of aerobic PA on type 2 diabetes risk. With the exception of NHBs, a similar magnitude of protection was found comparing the most active to the least active groups, ranging from 24% (among Asians) to 29% (among NHWs). The summary estimate for NHBs, though protective, did not attain statistical significance. The results of this analysis add to the existing literature on PA and type 2 diabetes (6, 10) by demonstrating effect modification by race-ethnicity.

Previous work (7, 41-43) has also found that there may be race-ethnicity specific differences in the volume of aerobic PA necessary to elicit protection against type 2 diabetes. Celis-Morales et al. (41) found that Asian men needed 266 min/wk of moderate aerobic PA in order to achieve similar cardiometabolic profiles (inclusive of fasting glucose and fasting insulin) as NHW men participating in 150 min/wk of moderate aerobic PA. Steinbrecher et al. (42), in a study contrasting race-ethnic specific differences of type 2 diabetes risk with PA, found that moderate intensity PA was associated with lower risk for type 2 diabetes only among NHW males and females. In the same study, Native Hawaiians and Japanese Americans were found to receive no protection from moderate intensity PA. However, vigorous intensity sport activity was associated with lower risk for type 2 diabetes across all race-ethnic groups independent of gender. These results indicate that higher volumes, as well as a higher intensity, may be needed to provide similar protection from type 2 diabetes across various race-ethnic groups.

Among the studies included the current analysis, five studies directly reported the race-specific RRs based upon meeting versus not meeting the current DHHS moderate-intensity aerobic PA recommendation and type 2 diabetes risk. The summary results of these studies

suggest a trend towards significant protection against type 2 diabetes for Asians and NHWs, but not NHBs or Hispanics. While these results need to be interpreted with caution, this illustrates a lack of studies specifically examining how meeting the current moderate-intensity aerobic PA guideline relates to type 2 diabetes risk. Previous work in the Diabetes Prevention Program (5) (designed to examine how lifestyle change inclusive of PA, dietary change and weight loss impacts type 2 diabetes risk) indicated that lifestyle intervention, inclusive of 150 min/wk of moderate aerobic PA, significantly reduced the incidence of type 2 diabetes in NHWs, NHBs, Asians, Hispanics and American Indians. It is possible that meeting the recommendations may not have a significant impact on diabetes risk reduction among NHBs without the addition of weight loss and dietary intervention; however more research is needed.

The discussion above, in addition to the results of the current meta-analysis, prompted the current authors to examine/review possible underlying physiological mechanisms that explain the race-ethnic differences in the protective role of PA. Further, the current results warranted specific focus on these mechanisms in NHBs.

**Mechanisms proposed**

There are several physiological mechanisms proposed that could explain the lack of significance found for NHBs in the current analysis. These include: 1) genetic predisposition, 2) compromised hepatic suppression of endogenous glucose production (EGP) in response to insulin, 3) lower insulin sensitivity ($S_i$) in the peripheral tissues (specifically skeletal muscle) despite similar volumes of aerobic PA, 4) a down regulation of insulin receptors driven by hyperinsulinemia and decreased hepatic insulin clearance, 5) increases in intramuscular adipose tissue (IMAT) and intra-myocellular lipid content (IMCL) deposits, and 6) skeletal muscle fiber type differences.

It is well known that decreases in $S_i$ are related to an increased risk for type 2 diabetes (44, 45). Lakoski and colleagues (46), when comparing NHBs to NHWs, found similar changes in the homeostatic model assessment of insulin resistance (HOMA-IR) for every 10 minute increase in MVPA, moderate PA, or vigorous PA. Among NHB and NHW women, Irwin and colleagues (47) reported similar decreases in fasting insulin levels for every 90 MET-min/d change. Another study conducted by Hasson et al. (48) found no differences in the acute improvements in whole-body $S_i$ comparing NHBs to NHWs following a single 75 minute bout of exercise at 75% VO2 max. The results of these studies indicate that NHBs and NHW have similar physiological responses in the change in $S_i$ from PA. However, similar levels of $S_i$ among NHWs and NHBs may not be indicative of similar risk profiles for type 2 diabetes as other factors may contribute.

**1. Genetic predisposition**

Despite the similar changes in $S_i$ in response to PA, NHBs tend to have lower initial Si compared to NHWs (49-51); which may contribute to the lack of significance found in the current study. Further explanation of this potential increased susceptibility to diabetes is associated with the relationship between whole-body $S_i$ and insulin response in NHBs compared to NHW and Asians. In a recent systematic review, Kodama et al. (50) calculated and illustrated the relationship between whole-body $S_i$ and the acute-insulin response to glucose (AIRg). Specifically in NHBs with normal glucose tolerance (NGT), the authors concluded that due to the relationship found between $S_i$ and AIRg, even the slightest decrease in $S_i$ results in large nonlinear increases in AIRg which plays a role in the progression towards type 2 diabetes. In contrast, these changes in $S_i$ among NHWs and Asians result in a vastly lower magnitude of changes in AIRg. In other words, among NHBs, the slightest decrease in $S_i$ results in a large

increase in the volume of insulin needed to maintain normal blood glucose. Furthermore, NHBs with similar $S_i$ values had significantly higher AIRg compared to NHWs. This relationship was further confirmed in a study by Albu et al. (52) which found higher AIRg in NHBs during an intravenous-glucose-tolerance test independent of $S_i$, visceral adipose tissue, intramuscular adipose tissue (IMAT), subcutaneous adipose tissue, and skeletal muscle mass. Thus Kodama et al. (50) and Albu et al. (52) conclude there is underlying genetic phenotype in NHBs that may predispose them to increased risk to type 2 diabetes reflected by this relationship.

**2. Hepatic influence**

Previous research examining the potential mechanism behind why NHBs are at a higher risk for type 2 diabetes has focused on the contributions of hepatic glycemic function. Insulin acts primarily on the peripheral tissues but also has inhibitory effects on hepatic endogenous glucose production (EGP) (53, 54). EGP has been shown to be the primary determinant of glucose tolerance (55) as well as a contributor to the development of type 2 diabetes (56). The aforementioned mechanisms may contribute to the lack of significant findings for NHBs in the current meta-analysis. While still controversial, a review by Gaillard et al. (57) suggested that impaired EGP may be a contributing factor to the increased susceptibility of NHBs to type 2 diabetes compared to NHWs. Moreover, in studies that showed similar EGP between NHBs and NHWs, AIRg tended to be higher in NHBs which is indicative of the increased compensation of the pancreatic β-cells to secrete more insulin. Thus, while EGP is linked to increased risk for type 2 diabetes, this proposed mechanism may not be a driving factor as results are equivocal.

**3. Peripheral $S_i$**

A review by Gaillard et al. (57) showed that while hepatic $S_i$ differences between NHBs and NHWs remains uncertain, peripheral $S_i$ tends to be lower among NHBs. With the established

association between type 2 diabetes risk and peripheral $S_i$; another mechanism to describe the findings of the current study is a diminished response of the skeletal muscle to changes in peripheral $S_i$. Delany et al. (43) revealed that participation in similar volumes of objectively measured PA (via upper extremity activity monitors), peripheral $S_i$ (calculated by dividing the rate of glucose disposal by the plasma insulin concentration) was 26% lower in NHBs compared to NHWs in the absence of obesity. Furthermore, hepatic $S_i$ as well as EGP was similar between groups. Haffner et al. (58) found lower peripheral $S_i$ (quantified by insulin-mediated glucose-disposal) independent of aerobic PA. The results of these studies indicate that aerobic PA may not affect peripheral $S_i$ in the same manner that it affects hepatic $S_i$, especially in NHBs, which could explain the lack of significance found in the current analysis. However, more research is warranted to confirm.

**4. Hepatic Insulin Clearance**

The consistent findings (50, 57) that show NHBs have higher AIRg compared to NHWs even with similar values of $S_i$ could also explain the differences seen in peripheral $S_i$. Higher AIRg is related to decreases in hepatic insulin clearance (50, 59). Gaillard et al. (57) suggested that the compensatory hyperinsulinemic response to a diminished hepatic insulin clearance may contribute to the down-regulation of the skeletal muscle insulin receptors. This would directly lead to decreases in peripheral $S_i$. It can also be postulated that this mechanism would manifest independent of aerobic PA as aerobic PA does not seem to impact AIRg in the same way as is does hepatic $S_i$. However, as stated by Gaillard et al. (57) this needs further exploration.

**5. Skeletal muscle adiposity**

One mechanism that may influence the decreased peripheral $S_i$ in NHBs is IMAT and intra-myocellular lipid content (IMCL). IMAT, defined as the adipose tissue found within the

muscle fascia, has been linked to a decrease in $S_i$ through inhibition of the insulin signaling pathway (60) leading to compromised insulin-stimulated glucose uptake and decreased $S_i$. A recent study by Goedecke et al. (61) showed that, in NHB women, increased IMCL defined as the accumulation of lipid particles within the muscle cell, and muscle fat % (IMAT) in the soleus were significantly correlated with lower $S_i$. NHW women had no relationship between IMCL and $S_i$. It is important to note that dietary habits and PA volume were similar between groups. Albu et al. (52) showed that despite similar overall associations, NHB women had significantly lower $S_i$ across volumes of IMAT compared to NHWs. Furthermore, the study participants had similar PA volumes. The results of these studies indicate that independent of PA, the increase in skeletal muscle lipid content may play a role in the decreased peripheral $S_i$ observed in NHBs. However, Ingram et al. (62) found conflicting evidence in NHB participants who had no significant correlation between IMCL and decreased peripheral Si; but NHWs did. Study participants were sedentary and no differences were found in regards to PA between groups. While this mechanism may explain differences in peripheral $S_i$ and perhaps the lack of significance in the current study, more research is needed to isolate the true effects of skeletal muscle lipid accumulation on $S_i$ and type 2 diabetes risk.

**6. Skeletal muscle fiber type**

Another mechanism that could contribute to lower $S_i$ and compromised glucose control (63), is a higher percentage of type II skeletal muscle fibers that can be found among NHBs compared to NHWs. Previous research contrasting race-ethnic groups has suggested a potential predisposition to an increased risk for type 2 diabetes with higher percentages of type II fibers (63, 64). More specfically, among lean, obese or particpants with type 2 diabetes, type I fibers have been shown to have a higher expression of GLUT4, a greater insulin-stimulated glucose

disposal rate, higher glucose oxidation rates and higher nonoxidative glucose metabolism compared to type II fibers (65). Interestingly, the expression of proteins specifc to the effects of insulin were similar across fiber types i.e. phosphoregulation. However, the study suggests that there needs to be more research to examine how phosphoregulation itself relates to glucose uptake and similar phosphoregulation might not mediate $S_i$ differences between fiber types. These results were futher confirmed by Daugaard et al. (66) who showed that only type I fibers had a significant increase in the expression of GLUT4 compared to both IIa and IIx fibers following two weeks of one-leg knee extensor training at 65% of maximum workload. The authors also conclude that increasing the intensity of the activity could have led to different findings i.e. changes in GLUT4 expression among Type II fibers. Thus, PA at higher intensities may be necessary to elicit the same benefits as those with higher percentages of type I fibers (64). However, more research is needed to confirm this hypothesis especially among NHBs. Nevertheless, among NHBs there is evidence to suggest that the biochemical differences between type I and type II fibers coupled with a higher percentage of type II fibers may help partially explain the findings of the current study.

**Limitations**

This study is not without limitations. First, all meta-analyses are subject to potential publication bias (39). We attempted to examine potential bias using a funnel plot procedure, which revealed no issues in regards to potential publication bias. Nonetheless, this issue is inherent to the systematic review process. Another limitation is that PA was self-reported in the studies used with the exception of one which used pedometers. Previous literature has shown limitations to using self-reported PA measures which may overestimate time spent in MVPA as well as failure to capture other intensities or sporadic activity (67, 68). Also, the lack of studies

specifically examining the relationship between PA and type 2 diabetes using the current DHHS aerobic PA recommendation does not provide enough evidence to clearly draw conclusions. The final limitation relates to inherent issues regarding the definitions of race-ethnicity (69). More specifically, only four of the definitions we used are considered to be race (NHB, NHW, Asian, and American Indian) and one is considered to be ethnicity (Hispanic) (70). Furthermore, there were semi-heterogeneous definitions of "race" and "ethnicity" used across the studies in this analysis. The authors of the current study elected to group study participants into five common race-ethnic groups found in the literature to provide the best insight into the race-ethnic specific relationship between aerobic PA and type 2 diabetes risk.

**Future Directions**

In the current meta-analysis, there was an evident paucity of prospective cohort studies reporting race-ethnic specific RRs, specifically in NHBs (N=5), Hispanics (N=3), and American Indians (N=5). Sensitivity analyses revealed a complete loss of statistical significance when Hsia et al. (18) or Ma et al. (25) were removed from the model; thus the interpretability of the summary RR for Hispanics is drastically limited by the available literature. Therefore, priorities for future research in this area should include prospective cohort studies examining PA and type 2 diabetes among multi-ethnic cohorts to examine and report risk across race-ethnic groups (rather than using race-ethnicity as a confounding variable). Furthermore, due to the mechanisms discussed previously, it is also evident that specific intensities should be examined as intensity may play a role in reducing risk for type 2 diabetes in NHBs.

**Conclusion**

In conclusion, with the exception of NHBs, PA plays a significant role in reducing the

risk for type 2 diabetes across race-ethnic groups. Furthermore, the current study illustrates the need to continue investigating effect modification of relationship by race-ethnicity, as well as the need to examine the effect modification between the current aerobic PA guideline and type 2 diabetes risk by race-ethnicity. There are several complex, physiological mechanisms that may explain the findings of the current study, which suggest there may be different race-specific thresholds in regards to the minimum aerobic PA needed to significantly reduce the risk for type 2 diabetes. Future studies may lead to a re-examination of the current aerobic PA guideline for potential changes specific to race-ethnicity.

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## Appendix 3

## Yearly trends in diabetes-related mortality across NHW and NHB

The following table is adapted from the Centers for Disease Control and Prevention webpage: Age-Adjusted Death Rates for Hyperglycemic Crises as Underlying Cause per 100,000 Diabetic Population, by Race and Sex, United States, 1980–2009.

Table A3.1. Age-Adjusted Death Rates for Hyperglycemic Crises as Underlying Cause per 100,000 Diabetic Population, by Race and Sex, United States, 1980–2009

| Year | White | | | | Black | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | Females | | Males | | Females | |
| | Rate | SE | Rate | SE | Rate | SE | Rate | SE |
| **1980** | 50.4 | 3.3 | 36.2 | 1.7 | 97.4 | 14.2 | 64.9 | 7.1 |
| **1981** | 46.5 | 3.3 | 35.8 | 1.7 | 111.1 | 18.0 | 66.3 | 7.7 |
| **1982** | 44.7 | 3.2 | 34.7 | 2.4 | 108.7 | 20.6 | 67.9 | 10.4 |
| **1983** | 41.1 | 3.2 | 41.2 | 3.1 | 175.7 | 54.8 | 55.1 | 8.4 |
| **1984** | 44.6 | 3.4 | 33.1 | 2.0 | 133.2 | 33.1 | 53.7 | 8.0 |
| **1985** | 44.2 | 4.8 | 32.2 | 2.4 | 102.6 | 25.9 | 61.2 | 10.4 |
| **1986** | 39.9 | 4.1 | 34.8 | 2.6 | 97.9 | 20.9 | 61.2 | 14.9 |
| **1987** | 44.2 | 4.2 | 31.1 | 2.3 | 73.5 | 12.8 | 42.5 | 6.6 |
| **1988** | 46.6 | 3.7 | 35.3 | 2.1 | 116.4 | 18.8 | 52.3 | 6.3 |
| **1989** | 50.1 | 3.9 | 34.5 | 2.0 | 128.6 | 23.2 | 48.7 | 5.0 |
| **1990** | 42.2 | 3.6 | 28.9 | 1.6 | 137.3 | 40.8 | 53.4 | 5.7 |
| **1991** | 40.7 | 3.3 | 29.0 | 1.7 | 142.3 | 40.2 | 52.1 | 7.0 |
| **1992** | 39.6 | 3.0 | 23.0 | 1.3 | 103.3 | 24.1 | 43.2 | 6.4 |
| **1993** | 36.2 | 2.7 | 25.4 | 1.6 | 96.8 | 17.1 | 36.9 | 4.4 |
| **1994** | 41.1 | 3.4 | 25.0 | 1.6 | 81.4 | 13.7 | 45.1 | 6.0 |
| **1995** | 46.5 | 4.7 | 24.0 | 1.5 | 96.4 | 21.1 | 45.8 | 6.2 |
| **1996** | 46.1 | 4.2 | 21.2 | 1.2 | 78.5 | 14.2 | 40.5 | 5.1 |
| **1997** | 35.5 | 2.6 | 21.7 | 1.2 | 79.8 | 12.2 | 37.9 | 4.0 |

Table A3.1 continued

| Year | White | | | | Black | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | Females | | Males | | Females | |
| | Rate | SE | Rate | SE | Rate | SE | Rate | SE |
| **1998** | 32.1 | 2.0 | 20.0 | 0.9 | 85.0 | 11.2 | 32.9 | 2.8 |
| **1999** | 33.5 | 2.1 | 18.7 | 0.8 | 70.7 | 9.7 | 31.6 | 2.5 |
| **2000** | 30.4 | 1.8 | 17.0 | 0.7 | 67.1 | 7.8 | 27.1 | 1.9 |
| **2001** | 25.8 | 1.5 | 18.0 | 0.7 | 63.1 | 6.3 | 26.3 | 1.9 |
| **2002** | 32.9 | 1.9 | 16.4 | 0.6 | 61.7 | 6.3 | 25.9 | 1.9 |
| **2003** | 33.7 | 2.1 | 16.6 | 0.7 | 54.4 | 5.5 | 28.5 | 2.4 |
| **2004** | 27.5 | 1.6 | 14.1 | 0.7 | 55.4 | 5.9 | 27.9 | 2.0 |
| **2005** | 25.7 | 1.4 | 13.7 | 0.6 | 45.8 | 4.2 | 19.5 | 1.6 |
| **2006** | 22.8 | 1.5 | 13.4 | 0.7 | 53.8 | 5.6 | 20.3 | 1.6 |
| **2007** | 24.0 | 1.7 | 13.2 | 0.7 | 44.6 | 5.1 | 22.9 | 2.0 |
| **2008** | 21.2 | 1.4 | 14.1 | 0.7 | 47.5 | 6.4 | 19.6 | 1.6 |
| **2009** | 19.5 | 1.5 | 11.7 | 0.6 | 42.6 | 7.0 | 16.0 | 1.5 |

SE = Standard Error

## Appendix 4

## Age-specific MET cut-points in the 1996 Surgeon General's report on physical activity and health

Table A4.1. 1996 Surgeon General's Report on Physical Activity and Health

| | Intensity (METs) in healthy adults | | | |
|---|---|---|---|---|
| | **Young (20-39)** | **Middle aged (40-64)** | **Old (65-79)** | **Very old (80+)** |
| **Very light** | **<3.0** | **<2.5** | **<2.0** | **<1.25** |
| **Light** | **3.0-4.7** | **2.5-4.4** | **2.0-3.5** | **1.26-2.2** |
| **Moderate** | **4.8-7.1** | **4.5-5.9** | **3.6-4.7** | **2.3-2.95** |
| **Hard** | **7.2-10.1** | **6.0-8.4** | **4.8-6.7** | **3.0-4.25** |
| **Very Hard** | **≥10.2** | **≥8.5** | **≥6.8** | **≥4.25** |

## Appendix 5

## Supplementary tables for Part 4:

## Effect modification of the association between leisure-time aerobic physical activity and diabetes-related mortality by race-ethnicity: a population-based prospective study using NHANES III

Table A5.1. Demographic, Heath and Physical Activity characteristics of participants stratified by diabetes-related mortality status: NHANES III (N=10,717)

| Variables | Value[c] | | | | |
|---|---|---|---|---|---|
| | Alive or non-diabetes-related mortality (n=10,386) | | Diabetes-related mortality (n=331) | | $X^2$ |
| **Demographics** | | | | | |
| *Age (mean)* | 42.4 | (0.4) | 61.2 | (0.7)* | p<0.001 |
| *Gender (%)* | | | | | |
| Male | 48.3 | (0.6) | 50.4 | (4.7) | p<0.001 |
| Female | 51.7 | (0.6) | 49.6 | (4.7) | |
| *Education (%)* | | | | | |
| Less than high school | 20.2 | (0.9) | 40.4 | (4.2)* | |
| High school graduate | 34.8 | (0.8) | 38.4 | (4.9) | p<0.001 |
| Some college/college graduate | 45.0 | (1.3) | 21.2 | (4.6)* | |
| **Family History of Diabetes** *(%)* | | | | | |
| Yes | 22.5 | (0.7) | 43.8 | (4.3)* | p<0.001 |
| No | 77.5 | (0.7) | 56.2 | (4.3)* | |
| **Metabolic Markers** | | | | | |
| *Body Mass Index (kg/m$^2$)(mean)* | 26.5 | (0.1) | 30.6 | (0.6)* | p<0.001 |
| *Glycemic Status (%)* | | | | | |
| Diabetes (A1c ≥ 6.5%) | 3.5 | (0.3) | 48.9 | (3.5)* | |
| Pre-diabetes (A1c 5.7-6.5%) | 13.0 | (0.8) | 23.6 | (3.8) | p<0.001 |
| Euglycemic (A1c < 5.7%) | 83.5 | (1.0) | 27.5 | (4.0)* | |
| **Health Behaviors** | | | | | |
| *Healthy Eating Index (0-100)(mean)* | 63.1 | (0.3) | 65.1 | (1.0) | p=0.09 |
| *Smoking Status (%)* | | | | | |
| Current smoker | 39.9 | (0.9) | 30.9 | (3.7) | |
| Former | 27.6 | (0.7) | 39.0 | (3.9)* | p<0.01 |
| Non-smoker | 32.5 | (1.0) | 30.1 | (3.7) | |
| *Alcohol consumption (%)* | | | | | |
| Drinker (≥12 dks/yr) | 35.3 | (1.3) | 64.6 | (4.4)* | p<0.001 |
| Non-drinker (<12 dks/yr) | 64.7 | (1.3) | 35.4 | (4.4)* | |
| **Physical Activity** | | | | | |
| *Physical Activity Score (median)* | 12.6 | (3.6-29.2) | 5.4 | (0.5-3.4)* | p<0.001 |
| *Physical Activity Guideline Index (%)* | | | | | |
| Inactive[b] | 11.5 | (0.7) | 27.5 | (3.9)* | |
| Insufficiently Active (PAS ≥0-<10) | 44.5 | (1.1) | 39.3 | (4.4) | p<0.001 |
| Active (PAS ≥10) | 44.0 | (1.4) | 33.2 | (4.2) | |
| *Physical Activity Index (%)* | | | | | |
| Inactive[a] | 11.5 | (0.7) | 26.4 | (3.8)* | |
| Quartile 1 | 21.6 | (1.0) | 25.9 | (3.8) | |
| Quartile 2 | 22.6 | (0.6) | 14.3 | (2.3)* | p<0.001 |
| Quartile 3 | 22.1 | (0.8) | 23.3 | (4.3) | |
| Quartile 4 | 22.2 | (1.0) | 10.1 | (2.3)* | |

SE = Standard Error; PAS: Physical Activity Score; A1c: glycosylated hemoglobin; dks: drinks; yr: year

[a]Zero activity reported.

[b]Zero activity or only very light activity reported.

[c]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as weighted percentage (SE).

*significantly different (p<0.05) from "Alive or non-diabetes-related mortality"

Table A5.2. Diabetes-related mortality risk and the Physical Activity Guideline Index stratified by race-ethnicity: NHANES III (N=10,717)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Race-Ethnicity | | |
| | **NHW** | **NHB** | **MA** |
| | Fully-adjusted | Fully-adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *Physical Activity Guideline Index* | | | |
| Inactive | 1.00 | 1.00 | 1.00 |
| Insufficiently Active (PAS ≥0-10) | 0.51 (0.29-0.89)* | 0.62 (0.34-1.15) | 0.84 (0.59-1.19) |
| Active (PAS ≥10) | 0.57 (0.33-0.99)* | 0.56 (0.27-1.19) | 0.50 (0.23-1.09) |
| *Age* | 1.10 (1.18-1.13)* | 1.08 (1.06-1.11)* | 1.09 (1.06-1.11)* |
| *Gender* | | | |
| Male | 1.00 | 1.00 | 1.00 |
| Female | 0.86 (0.52-1.41) | 0.63 (0.33-1.21) | 0.65 (0.38-1.10) |
| *Education* | | | |
| Less than high school | 1.00 | 1.00 | 1.00 |
| High school graduate | 1.03 (0.65-1.66) | 1.14 (0.66-1.97) | 0.70 (0.36-1.39) |
| Some college/college graduate | 0.73 (0.35-1.52) | 0.80 (0.41-1.55) | 1.36 (0.66-2.79) |
| **Family History of Diabetes** | | | |
| Yes | 1.00 | 1.00 | 1.00 |
| No | 0.73 (0.49-1.13) | 0.91 (0.60-1.41) | 0.95 (0.57-1.57) |
| **Metabolic Markers** | | | |
| *Body Mass Index (kg/m$^2$)* | 1.05 (1.02-1.09) | 1.03 (0.99-1.08) | 1.04 (0.99-1.10) |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | 1.00 | 1.00 | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | 0.16 (0.09-0.28)* | 0.14 (0.07-0.31)* | 0.19 (0.10-0.35)* |
| Euglycemic (A1c < 5.7%) | 0.06 (0.03-0.11)* | 0.14 (0.06-0.30)* | 0.10 (0.07-0.17)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index (0-100)* | 1.00 (0.98-1.02) | 1.00 (0.99-1.03) | 1.01 (0.99-1.02) |
| *Smoking Status* | | | |
| Current smoker | 1.00 | 1.00 | 1.00 |
| Former | 0.40 (0.25-0.64)* | 0.55 (0.25-1.18) | 0.50 (0.27-0.93)* |
| Non-smoker | 0.45 (0.27-0.74)* | 0.35 (0.16-0.77)* | 0.23 (0.13-0.42)* |
| *Alcohol consumption* | | | |
| Drinker (≥12 dks/yr) | 1.00 | 1.00 | 1.00 |
| Non-drinker (<12 dks/yr) | 0.74 (0.45-1.20) | 0.62 (0.36-1.08) | 1.05 (0.58-1.91) |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American. *p<0.05

## Appendix 6

## Research question 1, part 2:

## Is there a dose-response relationship between self-reported quartiles of PA and diabetes-related mortality across race-ethnic groups?

Using the data from the NHANES III, a dose-response analysis was conducted using quartiles of PA. Using the methodology outlined in chapter 3, the physical activity scores (PAS) were then recoded into quartiles using the following methods:

Creation of five-level PA Index (PAI). The PAI was created to examine the dose-response relationship with diabetes-related mortality in NHANES III. Participants with a PAS of zero served as the referent group. The other four categories within the PAI were categorized using PAS quartiles. More specifically, the PAS quartiles were generated by excluding those with a "zero" PAS to find the PAS cut-points at the $25^{th}$, $50^{th}$ and $75^{th}$ percentiles. The cut-points for the PAI are as follows: Category 1 (PAS: 0), Category 2 (PAS: >0-5.46), Category 3 (PAS: 5.47-14.41), Category 4 (PAS: 14.42-31.32), and Category 5 (PAS: ≥31.33).

Table A6.4 displays the results of the analysis examining relationship between PA quartiles and the risk of diabetes-related mortality using race-ethnicity as a covariate. In the unadjusted analysis, significantly lower risk for diabetes-related mortality was found for all quartiles. Following adjustment for age and race-ethnicity, significance remained for quartiles 2 (HR 0.30, 95% CI 0.18-0.50), 3 (HR 0.54, 95% CI 0.33-0.91), and 4 (HR 0.23, 95% CI 0.13-0.40. Following further adjustment for all covariates, results remained significant for quartiles 2 (HR 0.41, 95% CI 0.24-0.68) and 4 (HR 0.38, 95% CI 0.22-0.64).

Tables A6.5 and A6.6 display the results of the analysis examining the effect modification of race-ethnicity on the relationship between PA quartiles and the risk of diabetes-related mortality. In the unadjusted analyses significantly lower risk for diabetes-related mortality was found across all quartiles in NHW and NHB. Significance was only found in the fourth quartile in MA. Following adjustment for covariates, NHW in quartiles 2 (HR 0.38, 95% CI 0.20-0.71) and 4 (HR0.35, 95% CI 0.20-0.34) had significantly lower risk for diabetes-related

mortality. Only NHB in the first quartile (HR 0.44, 95% CI 0.24-0.81) retained significance following further adjustment for covariates. In MA, significance remained in the fourth quartile (HR 0.36, 95% CI 0.16-0.81). A significant trend was found only for NHW.

The results of this analysis must be interpreted with caution for two reasons. First, the results of the Kaplan-Meier survival curves (not shown) indicated that the use of quartiles violated the proportional hazards assumption of the models. Second, due to the few deaths spaced across the quartiles of activity, the confidence intervals associated with each HR are large. It can be postulated that as more data becomes available from the NDI, the use of a more detailed dose-response (such as the quartiles) examination will become possible. Because of these two reasons, drawing conclusions from this analysis is not recommended.

## Physical Activity Quintile Characteristics

Table A6.1. Physical Activity characteristics of the participants: NHANES III (N=10,717)

| Variables | Value[b] | |
|---|---|---|
| **Physical Activity Quartiles** | | |
| *Physical Activity Index (%)* | | |
| Inactive[a] | 11.8 | (0.7) |
| Quartile 1 | 21.7 | (1.0) |
| Quartile 2 | 22.4 | (0.6) |
| Quartile 3 | 22.1 | (0.8) |
| Quartile 4 | 22.0 | (1.0) |

SE = Standard Error.
[a]Zero activity reported.
[b]Weighted percentage (SE).

Table A6.2 Physical Activity characteristics of participants stratified by diabetes-related mortality status: NHANES III (N=10,717)

| Variables | Value[b] | | | | |
|---|---|---|---|---|---|
| | **Alive or non-diabetes-related mortality (n=10,386)** | | **Diabetes-related mortality (n=331)** | | **$X^2$** |
| *Physical Activity Index (%)* | | | | | |
| Inactive[a] | 11.5 | (0.7) | 26.4 | (3.8)* | |
| Quartile 1 | 21.6 | (1.0) | 25.9 | (3.8) | |
| Quartile 2 | 22.6 | (0.6) | 14.3 | (2.3)* | p<0.001 |
| Quartile 3 | 22.1 | (0.8) | 23.3 | (4.3) | |
| Quartile 4 | 22.2 | (1.0) | 10.1 | (2.3)* | |

SE = Standard Error.
[a]Zero activity reported.
[b]Weighted percentage (SE).
*significantly different (p<0.05) from "Alive or non-diabetes-related mortal

Table A6.3. Physical Activity characteristics of participants stratified by race-ethnicity: NHANES III (N=10,717)

| Variables | Value[b] | | | | | | |
|---|---|---|---|---|---|---|---|
| | **NHW** | | **NHB** | | **MA** | | **$X^2$** |
| *Physical Activity Index (%)* | | | | | | | |
| Inactive[a] | 10.2 | (0.7) | 18.6 | (1.0)* | 24.4 | (1.4)*,^ | |
| Quartile 1 | 21.1 | (1.1) | 18.6 | (0.8) | 17.2 | (1.0) | |
| Quartile 2 | 23.1 | (0.7) | 20.3 | (0.7) | 19.5 | (1.1)*,^ | p<0.001 |
| Quartile 3 | 22.0 | (0.9) | 21.4 | (0.9)* | 18.8 | (1.0)* | |
| Quartile 4 | 22.6 | (1.1) | 21.1 | (1.2) | 20.1 | (1.1)* | |

SE = Standard Error.
[a]Zero activity reported.
[b]Weighted percentage (SE).
*significantly different (p<0.05) from NHW; ^significantly different from NHB.

Table A6.4. Diabetes-related mortality risk and the Physical Activity Index: NHANES III (N=10,717)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Unadjusted | Age and race-ethnicity adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *Physical Activity Index* | | | |
| Inactive | 1.00 | 1.00 | 1.00 |
| Q1 | 0.49 (0.31-0.76)* | 0.66 (0.43-1.02) | 0.65 (0.41-1.05) |
| Q2 | 0.22 (0.13-0.36)* | 0.30 (0.18-0.50)* | 0.41 (0.24-0.68)* |
| Q3 | 0.46 (0.27-0.77)* | 0.54 (0.33-0.91)* | 0.88 (0.52-1.50) |
| Q4 | 0.18 (0.11-0.30)* | 0.23 (0.13-0.40)* | 0.38 (0.22-0.64)* |
| **Demographics** | | | |
| *Age (years)* | | 1.11 (1.09-1.12)* | 1.10 (1.08-1.12)* |
| *Race-ethnicity* | | | |
| non-Hispanic white | | 1.00 | 1.00 |
| non-Hispanic black | | 1.47 (0.99-2.16) | 0.74 (0.51-1.06) |
| Mexican American | | 1.72 (1.21-2.47)* | 1.04 (0.69-1.55) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.78 (0.50-1.21) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 1.33 (0.74-2.41) |
| Some college/college graduate | | | 1.46 (0.77-2.77) |
| **Family History** | | | |
| *Family History of Diabetes* | | | |
| Yes | | | 1.00 |
| No | | | 0.76 (0.54-1.06) |
| **Metabolic Markers** | | | |
| *Body Mass Index (kg/m$^2$)* | | | 1.05 (1.02-1.08)* |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.17 (0.11-0.26)* |
| Euglycemic (A1c < 5.7%) | | | 0.07 (0.04-0.12)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index (0-100)* | | | 1.00 (0.99-1.02) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.42 (0.30-0.60)* |
| Non-smoker | | | 0.42 (0.28-0.64)* |
| *Alcohol consumption* | | | |
| Drinker (≥12 dks/yr) | | | 1.00 |
| Non-drinker (<12 dks/yr) | | | 0.73 (0.50-1.07) |

Q: Quartile. *p<0.05

Table A6.5. Diabetes-related mortality risk and the Physical Activity Index stratified by race-ethnicity: NHANES III (N=10,717)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Race-Ethnicity | | |
| | NHW | NHB | MA |
| | Fully-adjusted | Fully-adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *Physical Activity Index* | | | |
| Inactive | 1.00 | 1.00 | 1.00 |
| Q1 | 0.67 (0.38-1.15) | 0.44 (0.24-0.81)* | 0.74 (0.48-1.15) |
| Q2 | 0.38 (0.20-0.71)* | 0.63 (0.25-1.62) | 0.64 (0.32-1.28) |
| Q3 | 0.90 (0.46-1.76) | 0.75 (0.36-1.57) | 1.38 (0.78-2.41) |
| Q4 | 0.35 (0.20-0.34)* | 0.62 (0.24-1.57) | 0.36 (0.16-0.81)* |
| *Age* | 1.11 (1.08-1.13)* | 1.09 (1.06-1.11)* | 1.09 (1.07-1.11)* |
| *Gender* | | | |
| Male | 1.00 | 1.00 | 1.00 |
| Female | 0.82 (0.50-1.37) | 0.63 (0.33-1.20) | 0.62 (0.35-1.09) |
| *Education* | | | |
| Less than high school | 1.00 | 1.00 | 1.00 |
| High school graduate | 1.10 (0.72-1.69) | 1.12 (0.67-1.87) | 0.71 (0.37-1.38) |
| Some college/college graduate | 0.75 (0.37-1.53) | 0.77 (0.39-1.51) | 1.19 (0.58-2.43) |
| **Family History** | | | |
| *Family History of Diabetes* | | | |
| Yes | 1.00 | 1.00 | 1.00 |
| No | 0.73 (0.48-1.11) | 0.90 (0.58-1.37) | 0.92 (0.56-1.53) |
| **Metabolic Markers** | | | |
| *Body Mass Index (kg/m$^2$)* | 1.06 (1.02-1.09)* | 1.03 (0.99-1.07) | 1.05 (0.99-1.11) |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | 1.00 | 1.00 | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | 0.16 (0.10-0.28)* | 0.14 (0.07-0.30)* | 0.18 (0.09-0.34)* |
| Euglycemic (A1c < 5.7%) | 0.06 (0.03-0.11)* | 0.14 (0.06-0.30)* | 0.10 (0.06-0.16)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index (0-100)* | 1.00 (0.98-1.02) | 1.00 (0.99-1.03) | 1.01 (0.99-1.02) |
| *Smoking Status* | | | |
| Current smoker | 1.00 | 1.00 | 1.00 |
| Former | 0.40 (0.26-0.60)* | 0.53 (0.39-1.15) | 0.47 (0.25-0.88)* |
| Non-smoker | 0.44 (0.27-0.70)* | 0.35 (0.16-0.78)* | 0.22 (0.13-0.40)* |
| *Alcohol consumption* | | | |
| Drinker (≥12 dks/yr) | 1.00 | 1.00 | 1.00 |
| Non-drinker (<12 dks/yr) | 0.75 (0.48-1.19) | 0.60 (0.35-1.04) | 1.03 (0.57-1.84) |

Q: Quartile. *p<0.05

Table A6.6. The relationship between the physical activity index and diabetes-related mortality: NHANES III

| | Physical Activity Index | | | | | |
|---|---|---|---|---|---|---|
| | Inactive | Q1 | Q2 | Q3 | Q4 | p-for-trend |
| **Total** | | | | | | |
| Physical Activity Score | 0 | >0-<5.88 | ≥5.88-<14.93 | ≥14.93-<31.63 | ≥31.63 | |
| N | 1938 | 2131 | 2239 | 2266 | 2143 | |
| No. of deaths | 101 | 67 | 57 | 71 | 35 | |
| Person-years | 8809.83 | 17462.25 | 18397.42 | 18868.50 | 17470.33 | |
| Unadjusted HR | 1.00 | 0.49 (0.31-0.76) | 0.22 (0.13-0.36) | 0.46 (0.27-0.77) | 0.18 (0.11-0.30) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.65 (0.41-1.05) | 0.41 (0.24-0.68) | 0.88 (0.52-1.50) | 0.38 (0.22-0.64) | p=0.03 |
| **Non-Hispanic White** | | | | | | |
| Physical Activity Score | 0 | >0-<5.95 | ≥5.95-<15.29 | ≥15.29-<31.86 | ≥31.86 | |
| N | 550 | 971 | 1016 | 1061 | 965 | |
| No. of deaths | 31 | 31 | 20 | 29 | 16 | |
| Person-years | 8809.83 | 17462.25 | 18397.42 | 18868.50 | 17470.33 | |
| Unadjusted HR | 1.00 | 0.47 (0.28-0.80) | 0.19 (0.10-0.34) | 0.42 (0.22-0.80) | 0.17 (0.09-0.30) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.67 (0.38-1.15) | 0.38 (0.20-0.71) | 0.90 (0.46-1.76) | 0.35 (0.20-0.34) | p=0.05 |
| **Non-Hispanic Black** | | | | | | |
| Physical Activity Score | 0 | >0-<4.13 | ≥4.13-<13.80 | ≥13.80-<29.67 | ≥29.67 | |
| N | 586 | 610 | 616 | 644 | 601 | |
| No. of deaths | 32 | 15 | 12 | 21 | 8 | |
| Person-years | 9902.33 | 10854.75 | 11318.92 | 11588.42 | 11237.08 | |
| Unadjusted HR | 1.00 | 0.37 (0.21-0.67) | 0.36 (0.15-0.86) | 0.49 (0.24-0.99) | 0.22 (0.08-0.60) | p=0.01 |
| Adjusted HR[a] | 1.00 | 0.44 (0.24-0.81) | 0.63 (0.25-1.62) | 0.75 (0.36-1.57) | 0.62 (0.24-1.57) | p=0.52 |
| **Mexican American** | | | | | | |
| Physical Activity Score | 0 | >0-<3.54 | ≥3.54-<11.04 | ≥11.04-<27.69 | ≥27.69 | |
| N | 802 | 550 | 607 | 561 | 577 | |
| No. of deaths | 38 | 21 | 25 | 21 | 11 | |
| Person-years | 14672.58 | 10609.17 | 11440.50 | 10526.92 | 10836.92 | |
| Unadjusted HR | 1.00 | 0.71 (0.35-1.42) | 0.54 (0.29-1.00) | 0.86 (0.50-1.50) | 0.24 (0.11-0.51) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.74 (0.48-1.15) | 0.64 (0.32-1.28) | 1.38 (0.78-2.41) | 0.36 (0.16-0.81) | p=0.15 |

[a]Adjusted for: age, gender, education, family history of diabetes, body mass index, glycemic status, healthy eating index, smoking status, alcohol consumption. HR: Hazard Ratio. Q: Quartile

## Appendix 7

## Demographic charateristics of the 1999-2004 NHANES

Table A7.1. Baseline demographic, Heath and Physical Activity characteristics of the participants: 1999-2004 NHANES (N=3,327)

| Variables | Value[b] | |
|---|---|---|
| **Physical Activity** | | |
| *Met-min/wk (median)* | 688.2 | (161.2-1700.0) |
| *Physical Activity Guideline 3 (%)* | | |
| Inactive[a] | 16.1 | (1.19) |
| Insufficiently Active | 24.7 | (0.84) |
| Active | 59.2 | (1.40) |
| *Physical Activity Guideline 4 (%)* | | |
| Inactive[a] | 16.1 | (1.19) |
| Insufficiently Active | 24.7 | (0.84) |
| Active | 18.9 | (0.77) |
| High Active | 40.3 | (1.44) |
| *Physical Activity Quintiles (%)* | | |
| Inactive[a] | 16.1 | (1.19) |
| Quintile 1 | 16.4 | (0.78) |
| Quintile 2 | 17.1 | (0.81) |
| Quintile 3 | 16.9 | (0.85) |
| Quintile 4 | 16.4 | (0.82) |
| Quintile 5 | 17.3 | (0.85) |
| **Demographics** | | |
| *Age (mean)* | 55.6 | (0.24) |
| *Gender (%)* | | |
| Male | 49.4 | (0.90) |
| Female | 50.6 | (0.90) |
| *Education (%)* | | |
| Less than high school | 17.3 | (1.15) |
| High school graduate | 26.7 | (1.18) |
| Some college | 28.3 | (1.07) |
| College graduate | 27.7 | (1.46) |
| **Family History** | | |
| *Family History of Diabetes (%)* | | |
| Yes | 25.0 | (1.27) |
| No | 75.0 | (1.27) |
| **Metabolic Markers** | | |
| *Body Mass Index (kg/m$^2$)(mean)* | 28.6 | (0.18) |
| *Glycemic Status (%)* | | |
| Diabetes (A1c ≥ 6.5%) | 6.7 | (0.46) |
| Pre-diabetes (A1c 5.7-6.5%) | 16.4 | (1.06) |
| Euglycemic (A1c < 5.7%) | 76.9 | (1.21) |
| **Health Behaviors** | | |
| *Healthy Eating Index (0-100)(mean)* | 53.2 | (0.54) |
| *Smoking Status (%)* | | |
| Current smoker | 20.6 | (0.96) |
| Former | 35.0 | (0.98) |
| Non-smoker | 44.4 | (1.17) |
| *Alcohol consumption (%)* | | |
| Non-Drinker | 32.2 | (2.01) |
| Moderate | 58.8 | (1.77) |
| Above Moderate | 9.0 | (0.77) |

SE = Standard Error.

[a]Zero activity reported.

[b]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as percentage (SE). Alcohol consumption: Non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day)

*Physical Activity Guideline 3*: Inactive: 0 MET-min/wk; Insufficiently Active: >0-499 MET-min/wk; Active: ≥500 MET-min/wk.

*Physical Activity Guideline 4*: Inactive: 0 MET-min/wk; Insufficiently Active: >0-499 MET-min/wk; Active: 500-999 MET-min/wk; High Active: ≥1000 MET-min/wk.

Table A7.2. Demographic, Heath and Physical Activity characteristics of participants stratified by diabetes-related mortality status: 1999-2004 NHANES (N=3,327)

| Variables | Value[b] | | | |
|---|---|---|---|---|
| | Alive or non-diabetes-related mortality (n=3,265) | | Diabetes-related mortality (n=62) | |
| **Physical Activity** | | | | |
| *Met-min/wk (median)* | 695.9 | (168.8-1708.5) | 41.9 | (0-378.4)* |
| *Physical Activity Guideline 3 (%)* | | | | |
| Inactive[a] | 15.8 | (1.15) | 43.2 | (4.37)* |
| Insufficiently Active | 24.6 | (0.82) | 32.6 | (5.42) |
| Active | 59.7 | (1.37) | 24.2 | (2.11)* |
| *Physical Activity Guideline 4 (%)* | | | | |
| Inactive[a] | 15.7 | (1.15) | 43.2 | (4.37)* |
| Insufficiently Active | 24.6 | (0.82) | 32.6 | (5.42) |
| Active | 19.1 | (0.78) | 8.9 | (2.76)* |
| High Active | 40.6 | (1.41) | 15.3 | (2.31)* |
| *Physical Activity Quintiles (%)* | | | | |
| Inactive[a] | 15.8 | (1.15) | 43.2 | (4.37)* |
| Quintile 1 | 16.0 | (0.77) | 21.9 | (5.31) |
| Quintile 2 | 17.2 | (0.80) | 11.4 | (3.03) |
| Quintile 3 | 17.0 | (0.85) | 10.8 | (2.98) |
| Quintile 4 | 16.5 | (0.82) | 6.2 | (1.41)* |
| Quintile 5 | 17.5 | (0.84) | 6.4 | (2.28)* |
| **Demographics** | | | | |
| *Age (mean)* | 55.5 | (0.23) | 63.8 | (1.53)* |
| *Gender (%)* | | | | |
| Male | 50.6 | (0.93) | 53.8 | (5.24) |
| Female | 49.4 | (0.93) | 46.2 | (5.24) |
| *Education (%)* | | | | |
| Less than high school | 16.0 | (1.14) | 42.1 | (6.59)* |
| High school graduate | 26.7 | (1.19) | 27.0 | (4.29) |
| Some college | 28.3 | (1.08) | 27.1 | (5.09) |
| College graduate | 28.0 | (1.47) | 3.8 | (1.30)* |
| **Family History** | | | | |
| *Family History of Diabetes (%)* | | | | |
| Yes | 24.6 | (1.23) | 42.3 | (4.10)* |
| No | 75.4 | (1.23) | 57.3 | (4.10)* |
| **Metabolic Markers** | | | | |
| *Body Mass Index (kg/m$^2$)(mean)* | 28.5 | (0.18) | 31.0 | (1.42) |
| *Glycemic Status (%)* | | | | |
| Diabetes (A1c ≥ 6.5%) | 6.0 | (0.35) | 14.5 | (3.19)* |
| Pre-diabetes (A1c 5.7-6.5%) | 16.4 | (1.07) | 22.8 | (4.53) |
| Euglycemic (A1c < 5.7%) | 77.6 | (1.19) | 62.7 | (3.83)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index (0-100)(mean)* | 53.2 | (0.54) | 55.7 | (1.41) |
| *Smoking Status (%)* | | | | |
| Current smoker | 20.5 | (0.95) | 34.6 | (4.75)* |
| Former | 35.1 | (0.98) | 24.1 | (4.01)* |
| Non-smoker | 44.4 | (1.16) | 41.2 | (4.52) |
| *Alcohol consumption (%)* | | | | |
| Non-Drinker | 31.8 | (1.95) | 65.7 | (6.31)* |
| Moderate | 59.1 | (1.71) | 30.7 | (6.33)* |
| Above Moderate | 9.1 | (0.78) | 3.6 | (1.15)* |

SE = Standard Error

[a]Zero activity reported. [b]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as percentage (SE).

Alcohol consumption: Non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day)

*Physical Activity Guideline 3*: Inactive: 0 MET-min/wk; Insufficiently Active: >0-499 MET-min/wk; Active: ≥500 MET-min/wk.

*Physical Activity Guideline 4*: Inactive: 0 MET-min/wk; Insufficiently Active: >0-499 MET-min/wk; Active: 500-999 MET-min/wk; High Active: ≥1000 MET-min/wk.

*significantly different ($p<0.05$) from "Alive or non-diabetes-related mort

Table A7.3. Demographic, Heath and Physical Activity characteristics of participants stratified by race-ethnicity: 1999-2004 NHANES (N=3,327)

| Variables | Value[b] | | | |
|---|---|---|---|---|
| | NHW | | NHB | |
| **Physical Activity** | | | | |
| *Met-min/wk (median)* | 745.5 | (216.3-1770.3) | 278.6 | (0-1134.9)* |
| *Physical Activity Guideline 3 (%)* | | | | |
| Inactive[a] | 13.9 | (1.30) | 33.2 | (2.05)* |
| Insufficiently Active | 24.9 | (0.92) | 22.9 | (1.16) |
| Active | 61.2 | (1.50) | 43.9 | (2.06)* |
| *Physical Activity Guideline 4 (%)* | | | | |
| Inactive[a] | 13.9 | (1.30) | 33.2 | (2.05)* |
| Insufficiently Active | 24.9 | (0.93) | 22.9 | (1.16) |
| Active | 19.4 | (0.81) | 16.1 | (1.38) |
| High Active | 41.8 | (1.56) | 27.8 | (1.62)* |
| *Physical Activity Quintiles (%)* | | | | |
| Inactive[a] | 13.9 | (1.30) | 33.2 | (2.05)* |
| Quintile 1 | 16.4 | (0.84) | 13.4 | (1.05) |
| Quintile 2 | 17.7 | (0.91) | 12.8 | (1.07)* |
| Quintile 3 | 17.4 | (0.94) | 13.5 | (1.30) |
| Quintile 4 | 16.8 | (0.89) | 13.3 | (1.03) |
| Quintile 5 | 17.8 | (0.93) | 13.8 | (1.18) |
| **Demographics** | | | | |
| *Age (mean)* | 55.9 | (1.53) | 53.4 | (1.53)* |
| *Gender (%)* | | | | |
| Male | 51.1 | (0.99) | 47.6 | (1.75) |
| Female | 48.9 | (0.99) | 52.4 | (1.75) |
| *Education (%)* | | | | |
| Less than high school | 17.6 | (1.25) | 37.2 | (2.26)* |
| High school graduate | 27.2 | (1.35) | 23.6 | (1.77) |
| Some college | 28.6 | (1.20) | 25.9 | (1.58) |
| College graduate | 29.6 | (1.67) | 13.3 | (1.46)* |
| **Family History** | | | | |
| *Family History of Diabetes (%)* | | | | |
| Yes | 23.1 | (1.39) | 39.2 | (1.74)* |
| No | 76.9 | (1.39) | 60.8 | (1.74)* |
| **Metabolic Markers** | | | | |
| *Body Mass Index ($kg/m^2$)(mean)* | 28.3 | (1.42) | 30.2 | (1.42) |
| *Glycemic Status (%)* | | | | |
| Diabetes (A1c ≥ 6.5%) | 5.8 | (0.55) | 14.2 | (1.12)* |
| Pre-diabetes (A1c 5.7-6.5%) | 15.1 | (1.17) | 26.8 | (2.28)* |
| Euglycemic (A1c < 5.7%) | 79.1 | (1.37) | 59.0 | (1.41)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index (0-100)(mean)* | 53.7 | (1.41) | 49.5 | (1.41) |
| *Smoking Status (%)* | | | | |
| Current smoker | 19.4 | (1.07) | 30.5 | (1.61)* |
| Former | 36.8 | (1.03) | 21.4 | (1.21)* |
| Non-smoker | 43.8 | (1.30) | 48.1 | (1.67) |
| *Alcohol consumption (%)* | | | | |
| Non-Drinker | 30.8 | (2.29) | 43.2 | (1.77)* |
| Moderate | 60.0 | (2.02) | 49.1 | (2.02)* |
| Above Moderate | 9.2 | (0.86) | 7.7 | (1.17) |

SE = Standard Error

[a]Zero activity reported.

[b]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as percentage (SE). Alcohol consumption: Non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day)

*Physical Activity Guideline 3*: Inactive: 0 MET-min/wk; Insufficiently Active: >0-499 MET-min/wk; Active: ≥500 MET-min/wk.

*Physical Activity Guideline 4*: Inactive: 0 MET-min/wk; Insufficiently Active: >0-499 MET-min/wk; Active: 500-999 MET-min/wk; High Active: ≥1000 MET-min/wk.

*significantly different ($p<0.05$) from NHW.

## Appendix 8

**Among the 1999-2004 NHANES, is there a dose-response relationship between self-reported PA (3-level) and diabetes-related mortality across race-ethnic groups?**

Using the data from the 1999-2004 NHANES, a dose-response analysis was conducted using the 3-level PA (PAG3) variable outlined in chapter 3. Briefly, PA was coded into three categories based on the 2008 PA guidelines: 0 MET-minutes/wk (Inactive), <500 MET-minutes/wk (Insufficiently Active), ≥500 MET-minutes/wk which equates to meeting the 2008 DHHS aerobic PA guidelines of 150 minutes of MVPA/wk. Due to the overwhelming lack of diabetes-related mortality deaths in MA, the 1999-2004 analyses were conducted only in NHW and NHB. The results of the analyses are displayed in tables A8.1, A8.2 and A8.3.

The results in Table A8.1 reveal significantly lower risk for diabetes-related mortality in those who were insufficiently active (HR 0.47, 95% CI 0.26-0.84) or active (HR 0.14, 95% CI 0.08-0.27). Following adjustment for age and race-ethnicity, results remained significant for only active participants (HR 0.20, 95% CI 0.10-0.39). Following further adjustment for covariates, both insufficiently active (HR 0.54, 95% CI 0.34-0.86) and active (HR 0.58, 95% CI 0.36-0.94) participants had significantly lower risk for diabetes-related mortality.

Tables A8.2 and A8.3 illustrate the results of the analysis examining the relationship between the PAG3 and diabetes-related mortality stratified by race-ethnicity. In the unadjusted analysis for NHW, participants categorized as either insufficiently active (HR 0.46, 95% CI 0.22-0.99) or active (HR 0.14, 95% CI 0.07-0.30) had significantly lower risk for diabetes-related mortality compared to inactive participants. In NHB, only active participants had significantly lower risk (HR 0.19, 95% CI 0.06-0.59). Following further adjustment for covariates, results remained significant only for active NHW (HR 0.28, 95% CI 0.14-0.57). While not statistically significant, active NHB had a pronounced risk reduction that approached significance (HR 0.34, 95% CI 0.11-1.02). A significant p-for-trend was found for NHW (p=0.001) and NHB (p=0.04).

The results of the current analysis indicate that meeting the 2008 aerobic PA guidelines provides significant protection from diabetes-related mortality among those who are NHW. Among NHB, a clinically meaningful risk reduction was found among those who were active. However results did not attain statistical significance. Similar to the results found in the analysis using the NHANES III data, at a similar dose of activity (active PA), the risk reduction was similar between NHW and NHB. The overall low number of deaths related to diabetes and smaller sample size, especially in NHB, is likely contributing to the lack of significance and large confidence intervals found in the analysis.

When compared to the PA questionnaire in NHANES III, the 1999-2004 NHANES has the addition of duration as well as PA across different domains (i.e. transportation and domestic), thus providing researchers a more comprehensive examination of PA. Furthermore, the 1999-2006 NHANES also contains a questionnaire on muscular strengthening activity (MSA). Given the established effect of MSA on risk factors for diabetes-related mortality such as insulin sensitivity and glucose intolerance, the 1999-2006 NHANES provides the ability to examine how MSA relates to diabetes-related mortality. As more data are added to the NDI and subsequently the NHANES, it is likely the confidence intervals will decrease providing a better illustration of how PA relates to diabetes-related mortality.

Table A8.1. Relationship between the Physical Activity Guideline (3-level) and diabetes-related mortality: 1999-2004 NHANES (N=3,324)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Unadjusted | Age and race-ethnicity adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *Physical Activity Guideline 3* | | | |
| Inactive | 1.00 | 1.00 | 1.00 |
| Insufficiently Active | 0.47 (0.26-0.84)* | 0.63 (0.34-1.14) | 0.54 (0.34-0.86)* |
| Active | 0.14 (0.08-0.27)* | 0.20 (0.10-0.39)* | 0.58 (0.36-0.94)* |
| **Demographics** | | | |
| *Age (years)* | | 1.07 (1.04-1.10)* | 1.06 (1.01-1.11)* |
| *Race-ethnicity* | | | |
| NHW | | 1.00 | 1.00 |
| NHB | | 1.79 (0.94-3.41) | 0.80 (0.40-1.61) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.59 (0.33-1.05) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 0.90 (0.70-1.56) |
| Some college | | | 1.03 (0.43-2.50) |
| College graduate | | | 0.27 (0.05-1.57) |
| **Family History** | | | |
| *Family History of Diabetes* | | | |
| Yes | | | 1.00 |
| No | | | 0.59 (0.34-1.04) |
| *Body Mass Index ($kg/m^2$)* | | | 0.99 (0.93-1.06) |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.20 (0.10-0.44)* |
| Euglycemic (A1c < 5.7%) | | | 0.04 (0.01-0.13)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index (0-100)* | | | 1.01 (0.99-1.02) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.28 (0.11-0.71)* |
| Non-smoker | | | 0.44 (0.21-0.92)* |
| *Alcohol consumption* | | | |
| Non-drinker | | | 1.00 |
| Moderate | | | 0.56 (0.26-1.19) |
| Above moderate | | | 0.78 (0.25-2.45) |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American.
Physical Activity Guideline 3: Inactive: 0 MET-min/wk; Insufficiently Active: >0-<500 MET-min/wk; Active: ≥500 MET-min/wk.
Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).*p<0.05

Table A8.2. Relationship between the Physical Activity Guideline (3-level) and diabetes-related mortality stratified by race-ethnicity: 1999-2004 NHANES (N=3,324)

| Variables | Hazard Ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Race-Ethnicity | | | |
| | NHW | | NHB | |
| | Unadjusted | Fully-adjusted | Unadjusted | Fully-adjusted |
| **Physical Activity** | | | | |
| *Physical Activity Guideline 3* | | | | |
| Inactive | 1.00 | 1.00 | 1.00 | 1.00 |
| Insufficiently Active | 0.46 (0.22-0.99)* | 0.79 (0.39-1.60) | 0.61 (0.25-1.49) | 0.93 (0.30-2.18) |
| Active | 0.14 (0.07-0.30)* | 0.28 (0.14-0.57)* | 0.19 (0.06-0.59)* | 0.34 (0.11-1.02) |
| **Demographics** | | | | |
| *Age* | | 1.05 (0.99-1.12)* | | 1.08 (1.03-1.12)* |
| *Gender* | | | | |
| Male | | 1.00 | | 1.00 |
| Female | | 0.55 (0.26-1.17) | | 0.98 (0.34-2.73) |
| *Education* | | | | |
| Less than high school | | 1.00 | | 1.00 |
| High school graduate | | 1.18 (0.46-3.02) | | 0.51 (0.19-1.41) |
| Some college | | 1.52 (0.51-4.41) | | 0.12 (0.01-1.16) |
| College graduate | | 0.31 (0.04-2.60) | | 0.42 (0.05-3.38) |
| **Family History** | | | | |
| *Family History of Diabetes* | | | | |
| Yes | | 1.00 | | 1.00 |
| No | | 0.55 (0.26-1.15) | | 0.61 (0.24-1.55) |
| **Metabolic Markers** | | | | |
| *Body Mass Index (kg/m$^2$)* | | 1.00 (0.93-1.08) | | 0.92 (0.84-1.02) |
| *Glycemic Status* | | | | |
| Diabetes (A1c ≥ 6.5%) | | 1.00 | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | 0.19 (0.07-0.49)* | | 0.23 (0.08-0.62)* |
| Euglycemic (A1c < 5.7%) | | 0.03 (0.01-0.15)* | | 0.12 (0.04-0.38)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index* | | 1.01 (0.99-1.03) | | 1.00 (0.98-1.03) |
| *Smoking Status* | | | | |
| Current smoker | | 1.00 | | 1.00 |
| Former | | 0.31 (0.11-0.87)* | | 0.14 (0.04-0.53)* |
| Non-smoker | | 0.43 (0.16-1.15) | | 0.37 (0.15-0.91)* |
| *Alcohol consumption* | | | | |
| Non-drinker | | 1.00 | | 1.00 |
| Moderate | | 0.51 (0.20-1.31) | | 0.70 (0.33-1.50) |
| Above moderate | | 0.50 (0.05-4.93) | | 1.10 (0.25-4.92) |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American.
Physical Activity Guideline 3: Inactive: 0 MET-min/wk; Insufficiently Active: >0-<500 MET-min/wk; Active: ≥500 MET-min/wk.
Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).*p<0.05

Table A8.3. Hazards ratios from analyses examining the relationship between physical activity (3-level) and diabetes-related mortality: 1999-2004 NHANES

| | Physical Activity Guideline 3 | | | |
|---|---|---|---|---|
| | Inactive | Insufficiently Active | Active | p-for-trend |
| **MET-min/wk** | 0 | >0-<500 | ≥500 | |
| **Total** | | | | |
| N | 699 | 796 | 1832 | |
| No. of deaths | 29 | 17 | 16 | |
| Person-years | 5996.58 | 7151.50 | 16828.67 | |
| Unadjusted HR | 1.00 | 0.47 (0.26-0.84) | 0.14 (0.08-0.27) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.54 (0.34-0.86) | 0.58 (0.36-0.94) | p<0.001 |
| **Non-Hispanic White** | | | | |
| N | 369 | 580 | 1433 | |
| No. of deaths | 13 | 11 | 11 | |
| Person-years | 3066.50 | 5226.92 | 13269.50 | |
| Unadjusted HR | 1.00 | 0.46 (0.22-0.99) | 0.14 (0.07-0.30) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.79 (0.39-1.60) | 0.28 (0.14-0.57) | p=0.001 |
| **Non-Hispanic Black** | | | | |
| N | 330 | 215 | 399 | |
| No. of deaths | 16 | 6 | 5 | |
| Person-years | 2930.08 | 1913.67 | 3559.17 | |
| Unadjusted HR | 1.00 | 0.61 (0.25-1.49) | 0.19 (0.06-0.59) | p=0.002 |
| Adjusted HR[a] | 1.00 | 0.93 (0.30-2.18) | 0.34 (0.11-1.02) | p=0.04 |

[a]Adjusted for: age, gender, education, family history of diabetes, body mass index, glycemic status, healthy eating index, smoking status, alcohol consumption. HR: Hazard Ratio. Physical Activity Guideline 3: Inactive: 0 MET-min/wk; Insufficiently Active: >0-<500 MET-min/wk; Active: ≥500 MET-min/wk.

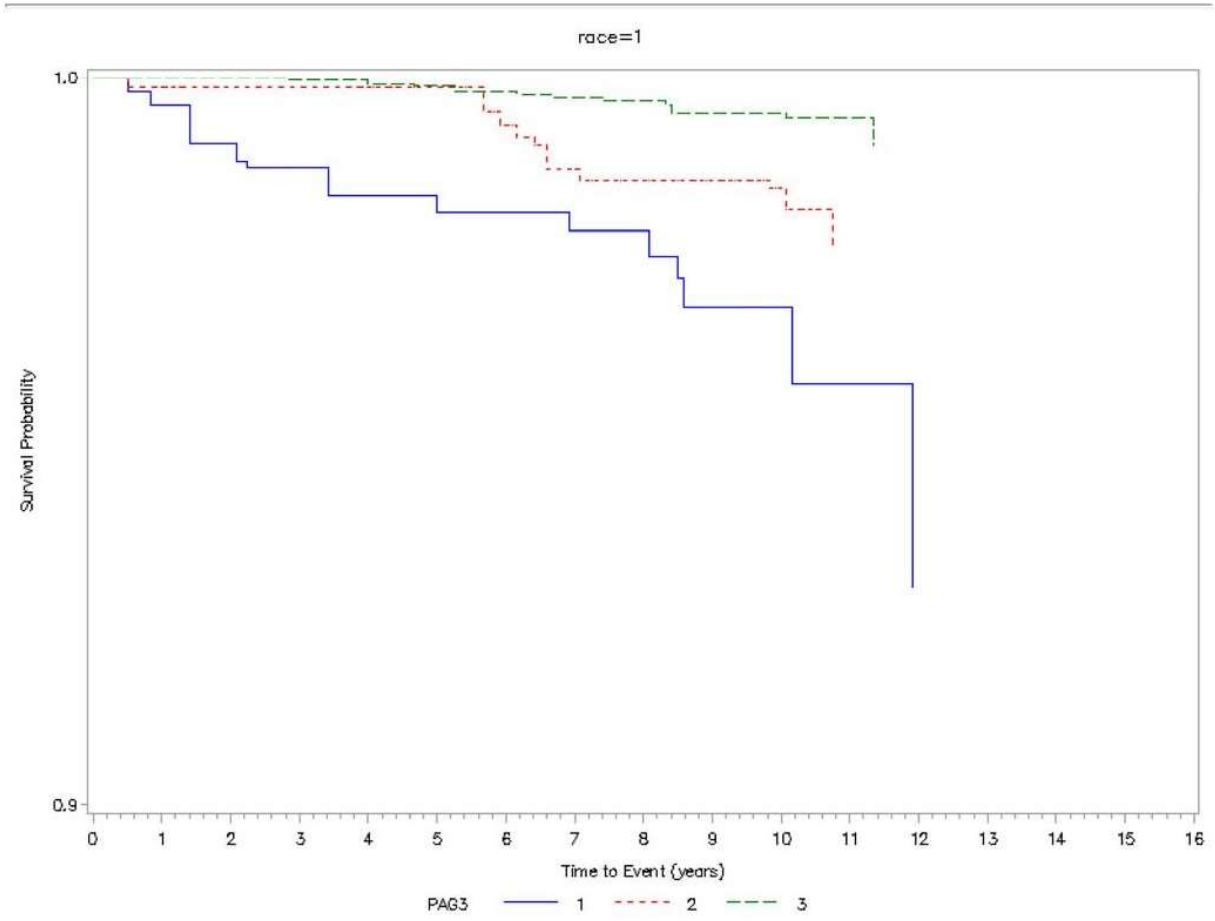


Figure A8.1. Kaplan-Meier Survival Curve: Physical Activity Guideline 3 and Non-Hispanic White

PAG3 1: Inactive; PAG3 2: Insufficiently Active; PAG3 3: Active

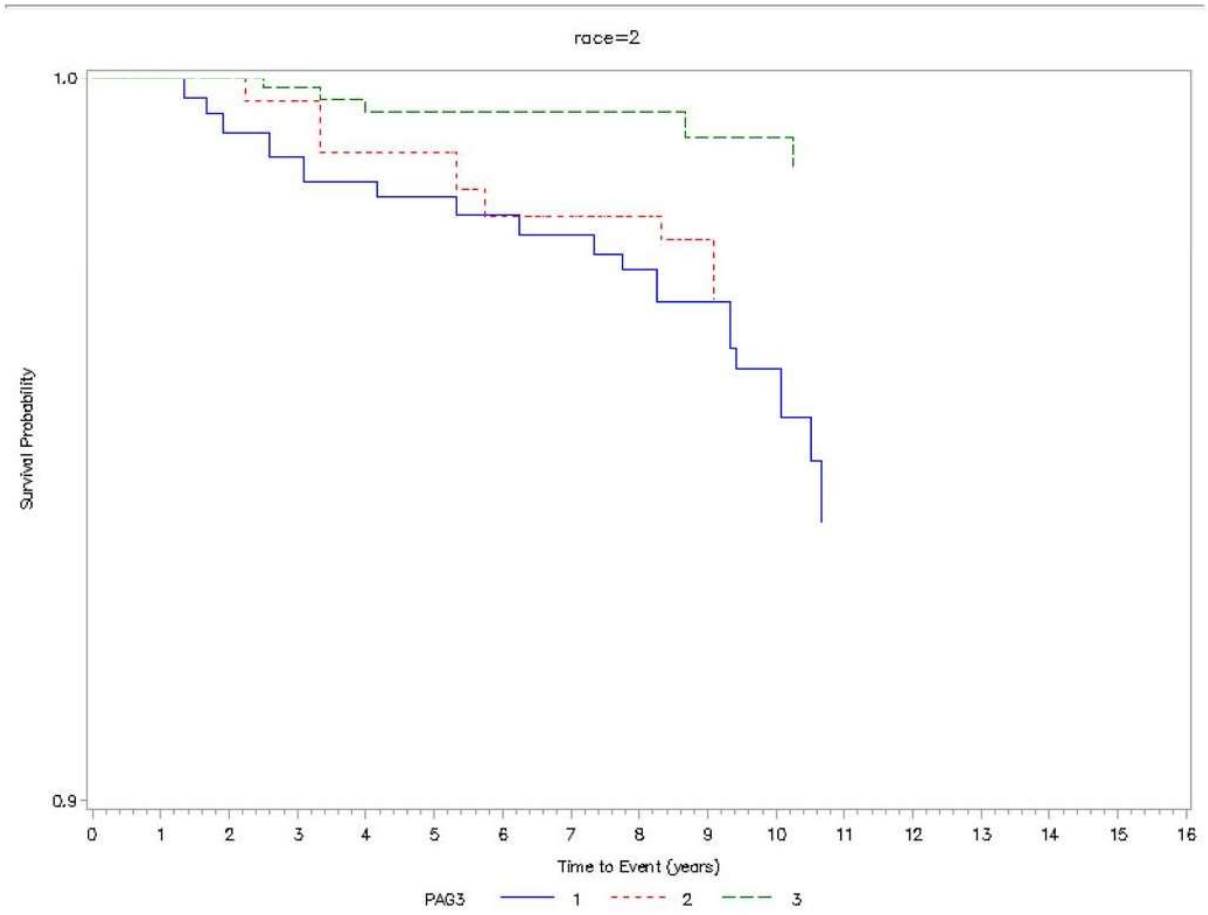


Figure A8.2. Kaplan-Meier Survival Curve: Physical Activity Guideline 3 and Non-Hispanic Black

PAG3 1: Inactive; PAG3 2: Insufficiently Active; PAG3 3: Active

## Appendix 9

**Among the 1999-2004 NHANES, is there a dose-response relationship between self-reported PA (4-level) and diabetes-related mortality across race-ethnic groups?**

Using the data from the 1999-2004 NHNAES, a dose-response analysis was conducted using the 4-level PA (PAG4) variable outlined in chapter 3. Briefly, PA was coded into four categories based on the 2008 PA guidelines: 0 MET-minutes/wk (Inactive), <500 MET-minutes/wk (Insufficiently Active), 500-<1000 MET-minutes/wk (Active) which equates to meeting the 2008 DHHS aerobic PA guidelines of 150 minutes of MVPA/wk and ≥1000 MET-minutes/wk (High active) which equates to volumes exceeding the recommendations of ≥300 minutes/wk of MVPA. The results of the analyses are displayed in tables A9.1, A9.2 and A9.3.

The results in Table A9.1 reveal significantly lower risk for diabetes-related mortality in those who were insufficiently active (HR 0.47, 95% CI 0.26-0.84), active (HR 0.17, 95% CI 0.08-0.36) or high active (HR 0.13, 95% CI 0.05-0.33). Following adjustment for age and race-ethnicity, results remained significant for insufficiently active (HR 0.24, 95% CI 0.11-0.52) and active participants (HR 0.18, 95% CI 0.07-0.48). Following further adjustment for covariates, both insufficiently active (HR 0.40, 95% CI 0.18-0.93) and active (HR 0.30, 95% CI 0.13-0.72) participants had significantly lower risk for diabetes-related mortality.

Tables A9.2 and A9.3 illustrate the results of the analysis examining the relationship between the PAG4 and diabetes-related mortality stratified by race-ethnicity. In the unadjusted analysis for NHW, participants categorized as either insufficiently active (HR 0.46, 95% CI 0.22-0.98), active (HR 0.14, 95% CI 0.05-0.41) or high active (HR 0.14, 95% CI 0.05-0.40) had significantly lower risk for diabetes-related mortality compared to inactive participants. In NHB, only high active participants had significantly lower risk (HR 0.05, 95% CI 0.01-0.38). Following further adjustment for covariates, results remained significant for high active NHW (HR 0.31, 95% CI 0.12-0.79) and NHB (HR 0.09, 95% CI 0.02-0.44). A significant p-for-trend was found for NHW (p=0.005) and NHB (p=0.01).

The results of the current analysis indicate that exceeding the 2008 aerobic PA guidelines (≥1000 MET-min/wk) provides significant protection from diabetes-related mortality among those who are NHW. Furthermore, the results indicate that meeting the 2008 aerobic guidelines of 500 MET-min/wk is not sufficient to provide protection. However, similar to the results examining the PAG3, there is a sufficient lack of power due to the small sample size and low amount of deaths related to diabetes. However, despite the lack of statistical power, there was still a significant trend for both NHW and NHB across increasing dose of PA. As more data become available from the NDI, the ability to examine thresholds based around the current PA guidelines will become obtainable.

Table A9.1. Relationship between Physical Activity Guideline (4-level) and diabetes-related mortality: 1999-2004 NHANES (N=3,324)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Unadjusted | Age and race-ethnicity adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *Physical Activity Guideline 4* | | | |
| Inactive | 1.00 | 1.00 | 1.00 |
| Insufficiently Active | 0.47 (0.26-0.84)* | 0.63 (0.34-1.14) | 0.76 (0.44-1.33) |
| Active | 0.17 (0.08-0.36)* | 0.24 (0.11-0.52)* | 0.40 (0.18-0.93)* |
| High Active | 0.13 (0.05-0.33)* | 0.18 (0.07-0.48)* | 0.30 (0.13-0.72)* |
| **Demographics** | | | |
| *Age (years)* | | 1.07 (1.04-1.10)* | 1.06 (1.01-1.11)* |
| *Race-ethnicity* | | | |
| NHW | | 1.00 | 1.00 |
| NHB | | 1.78 (0.94-3.40) | 0.80 (0.40-1.61) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.59 (0.33-1.05) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 0.90 (0.70-1.56) |
| Some college | | | 1.03 (0.43-2.50) |
| College graduate | | | 0.27 (0.05-1.57) |
| **Family History** | | | |
| *Family History of Diabetes* | | | |
| Yes | | | 1.00 |
| No | | | (0.57 (0.34-1.05) |
| **Metabolic Markers** | | | |
| *Body Mass Index (kg/m$^2$)* | | | 0.99 (0.93-1.06) |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.20 (0.10-0.44)* |
| Euglycemic (A1c < 5.7%) | | | 0.04 (0.01-0.13)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index* | | | 1.01 (0.99-1.02) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.28 (0.11-0.71)* |
| Non-smoker | | | 0.44 (0.21-0.92)* |
| *Alcohol consumption* | | | |
| Non-drinker | | | 1.00 |
| Moderate | | | 0.56 (0.26-1.19) |
| Above moderate | | | 0.78 (0.25-2.45) |

NHW: non-Hispanic white; NHB: non-Hispanic black;
Physical Activity Guideline 4: Inactive: 0 MET-min/wk; Insufficiently Active: >0-<500 MET-min/wk; Active: 500-999 MET-min/wk; High Active: ≥1000 MET-min/wk.
Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).*p<0.05

Table A9.2. Relationship between Physical Activity Guideline (4-level) and diabetes-related mortality stratified by race-ethnicity: 1999-2004 NHANES (N=3,324)

| Variables | Hazard Ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Race-Ethnicity | | | |
| | NHW | | NHB | |
| | Unadjusted | Fully-adjusted | Unadjusted | Fully-adjusted |
| **Physical Activity** | | | | |
| *Physical Activity Guideline 4* | | | | |
| Inactive | 1.00 | 1.00 | 1.00 | 1.00 |
| Insufficiently Active | 0.46 (0.22-0.98)* | 0.74 (0.37-1.50) | 0.61 (0.25-1.49) | 0.82 (0.31-2.18) |
| Active | 0.14 (0.05-0.41)* | 0.34 (0.10-1.10) | 0.46 (0.14-1.46) | 0.86 (0.22-3.39) |
| High Active | 0.14 (0.05-0.40)* | 0.31 (0.12-0.79)* | 0.05 (0.01-0.38)* | 0.09 (0.02-0.44)* |
| **Demographics** | | | | |
| *Age* | | 1.05 (0.99-1.12)* | | 1.08 (1.03-1.12)* |
| *Gender* | | | | |
| Male | | 1.00 | | 1.00 |
| Female | | 0.58 (0.26-1.18) | | 0.96 (0.34-2.73) |
| *Education* | | | | |
| Less than high school | | 1.00 | | 1.00 |
| High school graduate | | 1.18 (0.46-3.01) | | 0.48 (0.17-1.36) |
| Some college | | 1.50 (0.52-4.36) | | 0.11 (0.01-1.24) |
| College graduate | | 0.31 (0.03-2.91) | | 0.36 (0.06-3.37) |
| **Family History** | | | | |
| *Family History of Diabetes* | | | | |
| Yes | | 1.00 | | 1.00 |
| No | | 0.55 (0.76-1.15) | | 0.61 (0.24-1.56) |
| **Metabolic Markers** | | | | |
| *Body Mass Index (kg/m$^2$)* | | 1.00 (0.93-1.08) | | 0.92 (0.84-1.02) |
| *Glycemic Status* | | | | |
| Diabetes (A1c ≥ 6.5%) | | 1.00 | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | 0.19 (0.07-0.49)* | | 0.24 (0.08-0.68)* |
| Euglycemic (A1c < 5.7%) | | 0.03 (0.01-0.15)* | | 0.13 (0.04-0.41)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index* | | 1.01 (0.99-1.03) | | 1.01 (0.98-1.04) |
| *Smoking Status* | | | | |
| Current smoker | | 1.00 | | 1.00 |
| Former | | 0.31 (0.11-0.87)* | | 0.14 (0.03-0.54)* |
| Non-smoker | | 0.43 (0.16-1.15) | | 0.37 (0.15-0.91)* |
| *Alcohol consumption* | | | | |
| Non-drinker | | 1.00 | | 1.00 |
| Moderate | | 0.51 (0.20-1.31) | | 0.71 (0.32-1.62) |
| Above moderate | | 0.50 (0.05-5.14) | | 1.01 (0.23-4.44) |

NHW: non-Hispanic white; NHB: non-Hispanic black.
Physical Activity Guideline 4: Inactive: 0 MET-min/wk; Insufficiently Active: >0-<500 MET-min/wk; Active: 500-999 MET-min/wk; High Active: ≥1000 MET-min/wk.
non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).*p<0.05

Table A9.3. Hazards ratios from analyses examining the relationship between physical activity (4-level) and diabetes-related mortality: 1999-2004 NHANES

| | Physical Activity Guideline 4 | | | | |
|---|---|---|---|---|---|
| | Inactive | Insufficiently Active | Active | High Active | p-for-trend |
| **MET-min/wk** | 0 | >0-<500 | 500-<999 | ≥1000 | |
| **Total** | | | | | |
| N | 699 | 796 | 585 | 1247 | |
| No. of deaths | 29 | 17 | 8 | 8 | |
| Person-years | 3066.50 | 7151.50 | 5303.08 | 11525.58 | |
| Unadjusted HR | 1.00 | 0.47 (0.26-0.84) | 0.17 (0.08-0.36) | 0.13 (0.05-0.33) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.76 (0.44-1.33) | 0.40 (0.18-0.93) | 0.30 (0.13-0.72) | p=0.002 |
| **Non-Hispanic White** | | | | | |
| N | 369 | 580 | 442 | 990 | |
| No. of deaths | 13 | 11 | 4 | 7 | |
| Person-years | 3066.50 | 5226.92 | 4043.42 | 9217.58 | |
| Unadjusted HR | 1.00 | 0.46 (0.22-0.98) | 0.14 (0.05-0.41) | 0.14 (0.05-0.40) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.74 (0.37-1.50) | 0.34 (0.10-1.10) | 0.31 (0.12-0.79) | p=0.005 |
| **Non-Hispanic Black** | | | | | |
| N | 330 | 215 | 141 | 257 | |
| No. of deaths | 16 | 6 | 4 | 1 | |
| Person-years | 2930.08 | 1913.67 | 1239.58 | 2308.00 | |
| Unadjusted HR | 1.00 | 0.61 (0.25-1.49) | 0.46 (0.14-1.46) | 0.05 (0.01-0.38) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.82 (0.31-2.18) | 0.86 (0.22-3.39) | 0.09 (0.02-0.44) | p=0.01 |

[a]Adjusted for: age, gender, education, family history of diabetes, body mass index, glycemic status, healthy eating index, smoking status, alcohol consumption. HR: Hazard Ratio. Physical Activity Guideline 4: Inactive: 0 MET-min/wk; Insufficiently Active: >0-<500 MET-min/wk; Active: 500-999 MET-min/wk; High Active: ≥1000 MET-min/wk.

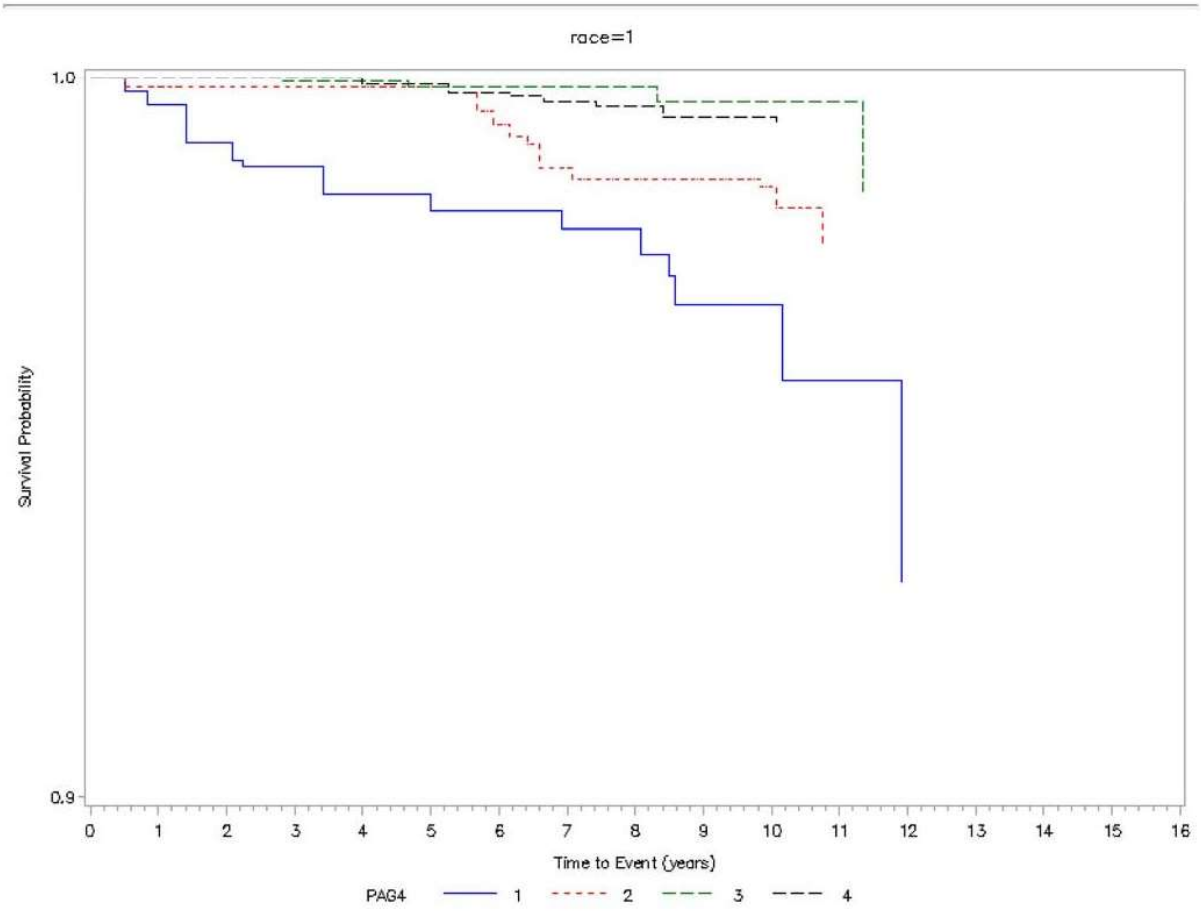


Figure 9.1. Kaplan-Meier Survival Curve: Physical Activity Guideline 4 and Non-Hispanic White

PAG4 1: Inactive; PAG4 2: Insufficiently Active; PAG4 3: Active; PAG4 4: High Active

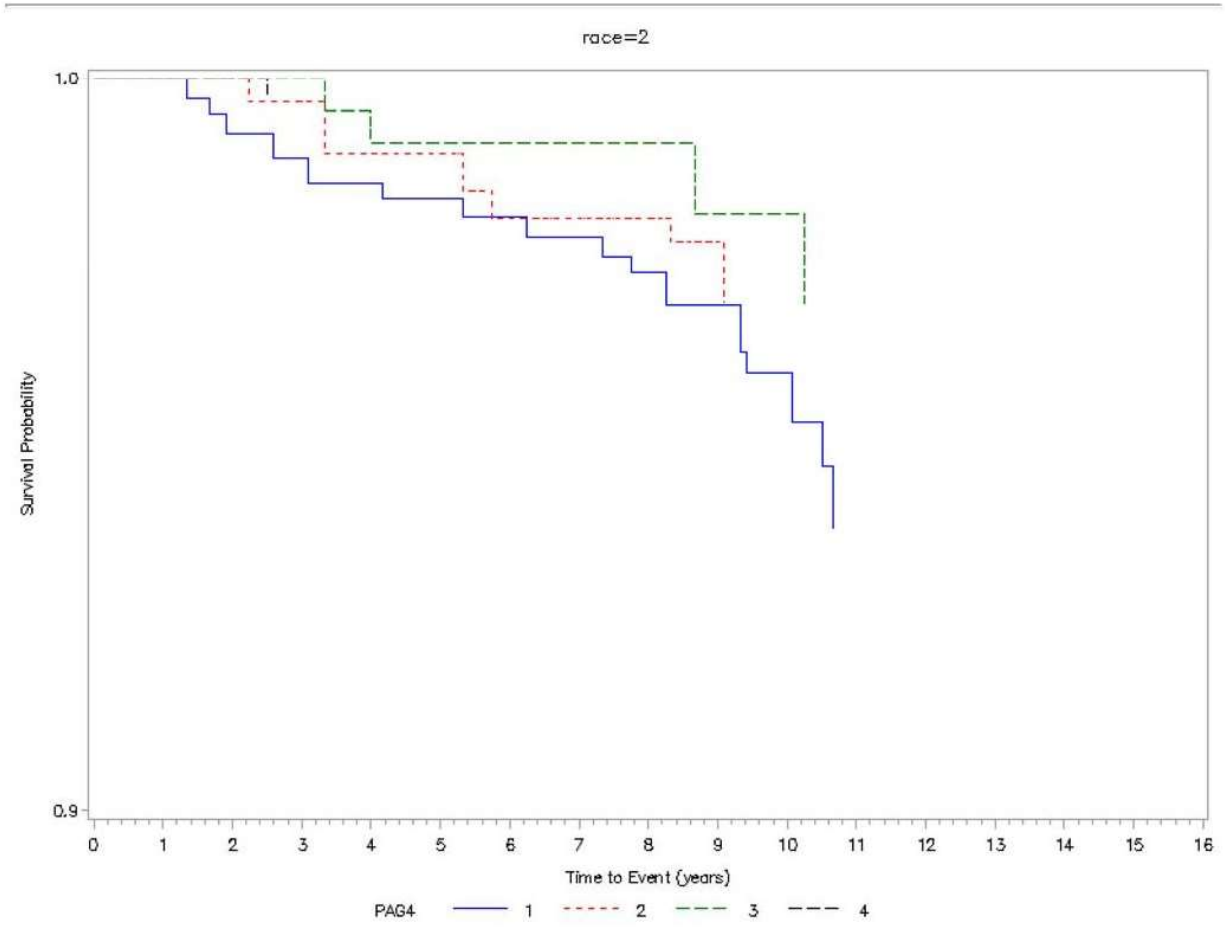


Figure 9.2. Kaplan-Meier Survival Curve: Physical Activity Guideline 4 and Non-Hispanic Black

PAG4 1: Inactive; PAG4 2: Insufficiently Active; PAG4 3: Active; PAG4 4: High Active

## Appendix 10

**Among the 1999-2004 NHANES, is there a dose-response relationship between self-reported quintiles of PA and diabetes-related mortality across race-ethnic groups?**

Table A10.1 displays the results of the analysis examining relationship between PA quintiles and the risk of diabetes-related mortality using race-ethnicity as a covariate. In the unadjusted analysis, significantly lower risk for diabetes-related mortality was found for all quintiles with the exception of quintile 1. Following adjustment for age and race-ethnicity, significance remained the same. Following further adjustment for all covariates, results remained significant for quintile 4 (HR 0.24, 95% CI 0.06-0.95).

Tables A6.5 and A6.6 display the results of the analysis examining the effect modification of race-ethnicity on the relationship between PA quartiles and the risk of diabetes-related mortality. In the unadjusted analyses, significantly lower risk for diabetes-related mortality was found across all quintiles in NHW except for quintile 1. Significance was only found in the fourth quintile in NHB. There were no deaths in quintile 5 therefore no hazard ratio could be calculated. Following adjustment for covariates, NHW in quartile 5 (HR 0.24, 95% CI 0.06-0.97) had significantly lower risk for diabetes-related mortality. No significant HR were found for NHB following adjustment for all covariates.

Similar to the analyses with the NHANES III quartiles in Appendix 6, the results of this analysis must be interpreted with caution. First, the results of the Kaplan-Meier survival curves (not shown) indicated that the use of quintiles violated the proportional hazards assumption of the models. Second, due to the few deaths spaced across the quartiles of activity, the confidence intervals associated with each HR are large. In quintile 5 for NHB, there were no deaths therefore no HR could be calculated. Thus, understanding the dose response relationship is severely diminished. It can be postulated that as more data becomes available from the NDI, the use of a more detailed dose-response (such as the quintiles) examination will become possible. Because of these reasons, drawing conclusions from this analysis is not recommended.

Table A10.1. Relationship between physical activity quintiles and diabetes-related mortality: 1999-2004 NHANES (N=3,324)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Unadjusted | Age and race-ethnicity adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *Physical Activity Quintiles* | | | |
| Inactive | 1.00 | 1.00 | 1.00 |
| Q1 | 0.49 (0.24-1.02) | 0.65 (0.31-1.35) | 0.69 (0.33-1.43) |
| Q2 | 0.23 (0.10-0.53)* | 0.33 (0.14-0.77)* | 0.67 (0.31-1.45) |
| Q3 | 0.22 (0.10-0.49)* | 0.33 (0.15-0.72)* | 0.49 (0.22-1.10) |
| Q4 | 0.14 (0.04-0.43)* | 0.19 (0.06-0.60)* | 0.38 (0.12-1.27) |
| Q5 | 0.13 (0.04-0.45)* | 0.17 (0.05-0.64)* | 0.24 (0.06-0.95)* |
| **Demographics** | | | |
| *Age (years)* | | 1.07 (1.04-1.10)* | 1.06 (1.01-1.11)* |
| *Race-ethnicity* | | | |
| NHW | | 1.00 | 1.00 |
| NHB | | 1.84 (0.97-3.51) | 0.80 (0.39-1.63) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.59 (0.32-1.07) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 0.88 (0.41-1.92) |
| Some college | | | 1.03 (0.43-2.46) |
| College graduate | | | 0.25 (0.04-1.40) |
| **Family History** | | | |
| *Family History of Diabetes* | | | |
| Yes | | | 1.00 |
| No | | | 0.59 (0.33-1.06) |
| **Metabolic Markers** | | | |
| *Body Mass Index (kg/m$^2$)* | | | 0.99 (0.93-1.06) |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.20 (0.09-0.44)* |
| Euglycemic (A1c < 5.7%) | | | 0.04 (0.01-0.13)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index* | | | 1.01 (0.99-1.02) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.27 (0.10-0.69)* |
| Non-smoker | | | 0.43 (0.20-0.91)* |
| *Alcohol consumption* | | | |
| Non-drinker | | | 1.00 |
| Moderate | | | 0.55 (0.25-1.18) |
| Above moderate | | | 0.79 (0.26-2.41) |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American. Q: Quintile.
Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).*p<0.05

Table A10.2. Relationship between physical activity quintiles and diabetes-related mortality stratified by race-ethnicity: 1999-2004 NHANES (N=3,324)

| Variables | Hazard Ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Race-Ethnicity | | | |
| | NHW | | NHB | |
| | Unadjusted | Fully-adjusted | Unadjusted | Fully-adjusted |
| **Physical Activity** | | | | |
| *Physical Activity Quintiles* | | | | |
| Inactive | 1.00 | 1.00 | 1.00 | 1.00 |
| Q1 | 0.46 (0.18-1.20) | 0.62 (0.25-1.57) | 0.86 (0.32-2.31) | 1.56 (0.55-4.43) |
| Q2 | 0.22 (0.09-0.59)* | 0.71 (0.27-1.82) | 0.37 (0.09-1.59) | 0.23 (0.02-3.13) |
| Q3 | 0.21 (0.08-0.54)* | 0.47 (0.18-1.22) | 0.37 (0.10-1.33) | 0.84 (0.19-3.74) |
| Q4 | 0.14 (0.04-0.51)* | 0.42 (0.10-1.67) | 0.11 (0.02-0.78)* | 0.23 (0.05-1.12) |
| Q5 | 0.15 (0.04-0.56)* | 0.24 (0.06-0.97)* | N/A | N/A |
| **Demographics** | | | | |
| *Age* | | 1.05 (0.99-1.12)* | | 1.08 (1.04-1.12)* |
| *Gender* | | | | |
| Male | | 1.00 | | 1.00 |
| Female | | 0.55 (0.26-1.17) | | 1.04 (0.33-3.22) |
| *Education* | | | | |
| Less than high school | | 1.00 | | 1.00 |
| High school graduate | | 1.16 (0.45-3.01) | | 0.41 (0.12-1.42) |
| Some college | | 1.49 (0.52-4.29) | | 0.10 (0.01-1.20) |
| College graduate | | 0.26 (0.03-2.36) | | 0.39 (0.04-3.67) |
| **Family History** | | | | |
| *Family History of Diabetes* | | | | |
| Yes | | 1.00 | | 1.00 |
| No | | 0.54 (0.26-1.17) | | 0.61 (0.24-1.55) |
| **Metabolic Markers** | | | | |
| *Body Mass Index (kg/m$^2$)* | | 1.00 (0.93-1.08) | | 0.92 (0.83-1.02) |
| *Glycemic Status* | | | | |
| Diabetes (A1c ≥ 6.5%) | | 1.00 | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | 0.18 (0.07-0.48)* | | 0.21 (0.07-0.67)* |
| Euglycemic (A1c < 5.7%) | | 0.03 (0.01-0.14)* | | 0.12 (0.04-0.33)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index* | | 1.01 (0.99-1.03) | | 1.01 (0.98-1.02) |
| *Smoking Status* | | | | |
| Current smoker | | 1.00 | | 1.00 |
| Former | | 0.29 (0.10-0.81)* | | 0.12 (0.03-0.47)* |
| Non-smoker | | 0.40 (0.15-1.11) | | 0.35 (0.14-0.88)* |
| *Alcohol consumption* | | | | |
| Non-drinker | | 1.00 | | 1.00 |
| Moderate | | 0.50 (0.19-1.31) | | 0.71 (0.31-1.63) |
| Above moderate | | 0.51 (0.05-5.00) | | 0.91 (0.17-4.92) |

NHW: non-Hispanic white; NHB: non-Hispanic black; MA: Mexican American. Q: Quintile
Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).*p<0.05

Table A10.3. Hazards ratios from analyses examining the relationship between physical activity (Quintiles) and diabetes-related mortality: 1999-2004 NHANES

| | Physical Activity Quintiles | | | | | | |
|---|---|---|---|---|---|---|---|
| | Inactive | Q1 | Q2 | Q3 | Q4 | Q5 | p-for-trend |
| **Total** | | | | | | | |
| MET-min/wk | 0 | >0-<312.34 | ≥312.34-<673.79 | ≥673.79-<1245.09 | ≥1245.09-<2382.52 | ≥2382.52 | |
| N | 699 | 515 | 528 | 512 | 514 | 559 | |
| No. of deaths | 29 | 11 | 7 | 8 | 4 | 3 | |
| Person-years | 5996.58 | 4546.58 | 4839.08 | 4748.00 | 4686.25 | 5160.25 | |
| Unadjusted HR | 1.00 | 0.49 (0.24-1.02) | 0.23 (0.10-0.53) | 0.22 (0.10-0.49) | 0.14 (0.04-0.43) | 0.13 (0.04-0.45) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.69 (0.33-1.43) | 0.67 (0.31-1.45) | 0.49 (0.22-1.10) | 0.38 (0.12-1.27) | 0.24 (0.06-0.95) | p=0.002 |
| **Non-Hispanic White** | | | | | | | |
| MET-min/wk | 0 | >0-<307.42 | ≥307.42-<682.35 | ≥682.35-<1258.91 | ≥1258.91-<2339.65 | ≥2339.65 | |
| N | 369 | 388 | 409 | 394 | 392 | 431 | |
| No. of deaths | 13 | 6 | 5 | 5 | 3 | 3 | |
| Person-years | 3066.50 | 3433.25 | 3766.83 | 3696.17 | 3596.50 | 4014.58 | |
| Unadjusted HR | 1.00 | 0.46 (0.18-1.20) | 0.22 (0.09-0.59) | 0.21 (0.08-0.54) | 0.14 (0.04-0.51) | 0.15 (0.04-0.56) | p<0.001 |
| Adjusted HR[a] | 1.00 | 0.62 (0.25-1.57) | 0.71 (0.27-1.82) | 0.47 (0.18-1.22) | 0.42 (0.10-1.67) | 0.24 (0.06-0.97) | p=0.008 |
| **Non-Hispanic Black** | | | | | | | |
| MET-min/wk | 0 | >0-<233.11 | ≥233.11-<560.52 | ≥560.52-<1022.72 | ≥1022.72-<2077.38 | ≥2077.38 | |
| N | 330 | 127 | 119 | 118 | 122 | 128 | |
| No. of deaths | 16 | 5 | 2 | 3 | 1 | 0 | |
| Person-years | 2930.08 | 1113.33 | 1072.25 | 1051.83 | 1089.75 | 1145.67 | |
| Unadjusted HR | 1.00 | 0.86 (0.32-2.31) | 0.37 (0.09-1.59) | 0.37 (0.10-1.33) | 0.11 (0.02-0.78) | - | p=0.002 |
| Adjusted HR[a] | 1.00 | 1.56 (0.55-4.43) | 0.23 (0.02-3.13) | 0.84 (0.19-3.74) | 0.23 (0.05-1.12) | - | p=0.009 |

[a]Adjusted for: age, gender, education, family history of diabetes, body mass index, glycemic status, healthy eating index, smoking status, alcohol consumption. HR: Hazard Ratio. Q: Quintile

## Appendix 11

## Demographic characteristics of the 2003-2006 NHANES

Table A11.1. Baseline demographic, Heath and Physical Activity characteristics of the participants: 2003-2006 NHANES (N=2,595)

| Variables | Value[a] | |
|---|---|---|
| **Physical Activity** | | |
| *MVPA 760 (median)* | 95.2 | (61.4–136.8) |
| *MVPA 2020 (median)* | 13.8 | (5.2-28.9) |
| *Total Activity Counts/d (%)* | | |
| Quartile 1 | 27.0 | (1.0) |
| Quartile 2 | 26.1 | (1.4) |
| Quartile 3 | 23.7 | (1.1) |
| Quartile 4 | 23.2 | (1.3) |
| **Demographics** | | |
| *Age (mean)* | 55.6 | (0.2) |
| *Gender (%)* | | |
| Male | 48.1 | (1.0) |
| Female | 51.9 | (1.0) |
| *Education (%)* | | |
| Less than high school | 11.9 | (1.5) |
| High school graduate | 27.4 | (0.9) |
| Some college | 32.3 | (1.2) |
| College graduate | 28.4 | (1.8) |
| **Metabolic Markers** | | |
| *Body Mass Index (kg/m$^2$)(mean)* | 28.6 | (0.2) |
| *Glycemic Status (%)* | | |
| Diabetes (A1c ≥ 6.5%) | 7.7 | (0.8) |
| Pre-diabetes (A1c 5.7-6.5%) | 19.5 | (0.9) |
| Euglycemic (A1c < 5.7%) | 72.8 | (1.2) |
| **Health Behaviors** | | |
| *Healthy Eating Index (0-100)(mean)* | 53.2 | (0.5) |
| *Smoking Status (%)* | | |
| Current smoker | 20.0 | (1.2) |
| Former | 33.7 | (1.2) |
| Non-smoker | 46.3 | (1.2) |
| *Alcohol consumption (%)* | | |
| Non-Drinker | 31.5 | (2.0) |
| Moderate | 59.7 | (1.7) |
| Above Moderate | 8.8 | (0.7) |

SE = Standard Error. MVPA 760 = moderate-to-vigorous minutes physical activity (≥760 counts/min). MVPA 2020 = moderate-to-vigorous minutes physical activity (≥2020 counts/min).

[a]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as percentage (SE). Alcohol consumption*:* non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day)

Table A11.2. Demographic, Heath and Physical Activity characteristics of participants stratified by diabetes-related mortality status: 2003-2006 NHANES (N=2,595)

| Variables | Value[c] | | | |
|---|---|---|---|---|
| | Alive or non-diabetes-related mortality (n=2,572) | | Diabetes-related mortality (n=23) | |
| **Physical Activity** | | | | |
| *MVPA 760 (median)* | 95.7 | (61.8-136.9) | 31.0 | (22.3-35.3)* |
| *MVPA 2020 (median)* | 13.8 | (5.3-28.9) | 1.7 | (1.2-3.6)* |
| *Total Activity Counts/d (%)* | | | | |
| Quartile 1 | 26.6 | (1.0) | 83.5 | (2.7)* |
| Quartile 2 | 26.2 | (1.4) | 2.7 | (0.2)* |
| Quartile 3 | 23.9 | (1.1) | 1.7 | (1.8)* |
| Quartile 4 | 23.3 | (1.3) | 12.1 | (1.0)* |
| **Demographics** | | | | |
| *Age (mean)* | 55.8 | (0.4) | 65.8 | (0.7)* |
| *Gender (%)* | | | | |
| Male | 48.0 | (1.0) | 62.9 | (7.8) |
| Female | 52.0 | (1.0) | 37.1 | (7.8) |
| *Education (%)* | | | | |
| Less than high school | 11.7 | (1.4) | 53.1 | (5.2)* |
| High school graduate | 27.5 | (0.9) | 22.0 | (1.7) |
| Some college | 32.3 | (1.2) | 22.5 | (5.6) |
| College graduate | 28.6 | (1.8) | 2.4 | (0.2)* |
| **Metabolic Markers** | | | | |
| *Body Mass Index (kg/m$^2$)(mean)* | 29.0 | (0.2) | 28.7 | (0.8) |
| *Glycemic Status (%)* | | | | |
| Diabetes (A1c ≥ 6.5%) | 7.4 | (0.7) | 66.5 | (7.5)* |
| Pre-diabetes (A1c 5.7-6.5%) | 19.4 | (0.9) | 31.7 | (7.6) |
| Euglycemic (A1c < 5.7%) | 73.2 | (1.2) | 1.8 | (0.1)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index (0-100)(mean)* | 49.1 | (0.5) | 43.5 | (2.1) |
| *Smoking Status (%)* | | | | |
| Current smoker | 20.0 | (1.2) | 30.7 | (4.6) |
| Former | 33.7 | (1.2) | 27.7 | (6.1) |
| Non-smoker | 46.3 | (1.2) | 41.6 | (5.1) |
| *Alcohol consumption (%)* | | | | |
| Non-Drinker | 31.2 | (2.0) | 76.8 | (7.2)* |
| Moderate | 59.9 | (1.7) | 21.3 | (7.2)* |
| Above Moderate | 8.9 | (0.7) | 1.9 | (0.2)* |

SE = Standard Error. MVPA 760 = moderate-to-vigorous physical activity (≥760 counts/min). MVPA 2020 = moderate-to-vigorous physical activity (≥2020 counts/min).

[a]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as percentage (SE). Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).

Table A11.3. Demographic, Heath and Physical Activity characteristics of participants stratified by race-ethnicity: 2003-2006 NHANES (N=2,595)

| Variables | Value[c] | | | |
|---|---|---|---|---|
| | NHW (n=1892) | | NHB (n=703) | |
| **Physical Activity** | | | | |
| *MVPA 760 (median)* | 95.6 | (62.0-136.9) | 92.7 | (53.4-134.8) |
| *MVPA 2020 (median)* | 14.3 | (5.4-29.4) | 11.1 | (4.2-25.1) |
| *Total Activity Counts/d (%)* | | | | |
| Quartile 1 | 26.4 | (1.1) | 31.5 | (1.7) |
| Quartile 2 | 26.1 | (1.6) | 26.4 | (1.5) |
| Quartile 3 | 23.8 | (1.2) | 23.7 | (1.8) |
| Quartile 4 | 23.7 | (1.4) | 18.4 | (1.3) |
| **Demographics** | | | | |
| *Age (mean)* | 56.0 | (0.4) | 54.2 | (0.4)* |
| *Gender (%)* | | | | |
| Male | 48.6 | (1.0) | 43.5 | (1.8) |
| Female | 51.4 | (1.0) | 56.6 | (1.8) |
| *Education (%)* | | | | |
| Less than high school | 10.4 | (1.6) | 25.2 | (1.7)* |
| High school graduate | 27.8 | (1.0) | 24.5 | (1.7) |
| Some college | 32.3 | (1.3) | 31.7 | (1.2) |
| College graduate | 29.5 | (1.9) | 18.6 | (1.7)* |
| **Metabolic Markers** | | | | |
| *Body Mass Index (kg/m$^2$)(mean)* | 28.8 | (0.2) | 30.8 | (0.3)* |
| *Glycemic Status (%)* | | | | |
| Diabetes (A1c ≥ 6.5%) | 6.7 | (0.8) | 16.2 | (1.8)* |
| Pre-diabetes (A1c 5.7-6.5%) | 18.1 | (1.0) | 31.7 | (1.8)* |
| Euglycemic (A1c < 5.7%) | 75.2 | (1.3) | 52.1 | (2.4)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index (0-100)(mean)* | 49.4 | (0.5) | 46.6 | (0.8)* |
| *Smoking Status (%)* | | | | |
| Current smoker | 19.5 | (1.3) | 25.0 | (2.3) |
| Former | 34.7 | (1.3) | 24.7 | (1.3)* |
| Non-smoker | 45.8 | (1.4) | 50.3 | (2.4) |
| *Alcohol consumption (%)* | | | | |
| Non-Drinker | 29.8 | (2.2) | 45.7 | (1.7)* |
| Moderate | 60.9 | (1.9) | 48.9 | (1.9)* |
| Above Moderate | 9.3 | (0.8) | 5.4 | (0.9)* |

SE = Standard Error. MVPA 760 = moderate-to-vigorous physical activity (≥760 counts/min). MVPA 2020 = moderate-to-vigorous physical activity (≥2020 counts/min).

[a]Median values expressed as median (Interquartile Range). Mean expressed as mean (SE). All other variables expressed as percentage (SE). Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day)

## Appendix 12

**3B. Is there a dose-response relationship between quartiles of accelerometer-derived total activity counts/day (TAC/d) and diabetes-related mortality across race-ethnic groups?**

The results of the analysis addressing research question 3B are displayed in tables 12.1, 12.2, and 12.3. In the unadjusted as well as the age and race-ethnicity adjusted analyses, significantly lower risk for diabetes-related mortality was found across all quartiles. Following further adjustment for covariates, significance remained only in quartile 3. In the race-ethnicity stratified analyses, a significantly lower risk for diabetes-related mortality was found only for quartile 4 in NHW. No relationships were found for NHB. Following further adjustment for covariates, results remained the same. Due to the significant lack of deaths, there was no ability to calculate hazard ratios in quartiles 2 and 3 for NHW and quartile 4 for NHB. This removes the ability to interpret the results in any way.

Table A12.1. Relationship between physical activity and diabetes-related mortality: 2003-2006 NHANES (N=2,595)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Unadjusted | Age and race-ethnicity adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *Total Activity Counts/day* | | | |
| Quartile 1 | 1.00 | 1.00 | 1.00 |
| Quartile 2 | 0.03 (0.01-0.17)* | 0.03 (0.01-0.18)* | 0.04 (0.01-0.19) |
| Quartile 3 | 0.02 (0.00-0.23)* | 0.02 (0.00-0.25)* | 0.04 (0.01-0.35)* |
| Quartile 4 | 0.17 (0.03-0.86)* | 0.18 (0.04-0.88)* | 0.30 (0.05-1.62) |
| **Demographics** | | | |
| *Age (years)* | | 1.09 (1.04-1.15)* | 1.06 (1.01-1.12)* |
| *Race-ethnicity* | | | |
| NHW | | 1.00 | 1.00 |
| NHB | | 1.82 (0.51-6.56) | 0.80 (0.40-1.61) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.48 (0.17-1.41) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 0.24 (0.70-1.56) |
| Some college | | | 0.51 (0.08-3.42) |
| College graduate | | | 0.07 (0.01-1.02) |
| **Metabolic Markers** | | | |
| *Body Mass Index* | | | 0.91 (0.85-0.98)* |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.21 (0.07-0.66)* |
| Euglycemic (A1c < 5.7%) | | | 0.01 (0.00-0.04)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index* | | | 0.97 (0.92-1.02) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.65 (0.16-2.68) |
| Non-smoker | | | 1.58 (0.57-4.47) |
| *Alcohol consumption* | | | |
| Non-drinker | | | 1.00 |
| Moderate | | | 0.45 (0.10-2.02) |
| Above moderate | | | 0.70 (0.06-8.53) |

NHW: non-Hispanic white; NHB: non-Hispanic black.
Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).
*p<0.05

Table A12.2. Relationship between physical activity and diabetes-related mortality stratified by race-ethnicity: 2003-2006 NHANES (N=2,595)

| Variables | Hazard Ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Race-Ethnicity | | | |
| | NHW | | NHB | |
| | Unadjusted | Fully-adjusted | Unadjusted | Fully-adjusted |
| **Physical Activity** | | | | |
| *Total Activity Counts/day* | | | | |
| Quartile 1 | 1.00 | 1.00 | 1.00 | 1.00 |
| Quartile 2 | No deaths | No deaths | 0.25 (0.06-1.04) | 0.18 (0.01-2.73) |
| Quartile 3 | No deaths | No deaths | 0.18 (0.02-1.78) | 0.29 (0.03-2.59) |
| Quartile 4 | 0.20 (0.04-1.06)* | 0.31 (0.12-0.79)* | No deaths | No deaths |
| **Demographics** | | | | |
| *Age* | | 1.06 (0.99-1.13) | | 1.12 (1.03-1.21)* |
| *Gender* | | | | |
| Male | | 1.00 | | 1.00 |
| Female | | 0.33 (0.10-1.11) | | 3.80 (1.27-11.43)* |
| *Education* | | | | |
| Less than high school | | 1.00 | | 1.00 |
| High school graduate | | 0.12 (0.01-1.00)* | | 1.34 (0.13-13.47) |
| Some college | | 0.53 (0.04-6.78) | | 0.34 (0.02-4.88) |
| College graduate | | No deaths | | 3.36 (0.06-193.48) |
| **Metabolic Markers** | | | | |
| *Body Mass Index* | | 0.93 (0.83-1.03) | | 0.87 (0.80-0.94)* |
| *Glycemic Status* | | | | |
| Diabetes (A1c ≥ 6.5%) | | 1.00 | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | 0.19 (0.07-0.49)* | | 0.24 (0.06-1.00)* |
| Euglycemic (A1c < 5.7%) | | No deaths | | 0.03 (0.00-0.84)* |
| **Health Behaviors** | | | | |
| *Healthy Eating Index* | | 0.96 (0.90-1.03) | | 1.01 (0.98-1.05) |
| *Smoking Status* | | | | |
| Current smoker | | 1.00 | | 1.00 |
| Former | | 0.85 (0.09-7.91) | | 0.96 (0.29-3.18) |
| Non-smoker | | 3.43 (1.00-11.83) | | 0.03 (0.00-0.75)* |
| *Alcohol consumption* | | | | |
| Non-drinker | | 1.00 | | 1.00 |
| Moderate | | 0.40 (0.05-3.08) | | 0.71 (0.32-1.62) |
| Above moderate | | No deaths | | 1.01 (0.23-4.44) |

NHW: non-Hispanic white; NHB: non-Hispanic black.
Alcohol consumption: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).
*p<0.05

Table A12.3. The relationship between total activity counts/day quartiles and diabetes-related mortality: NHANES III

| | Total Activity Counts/day quartiles | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | p-for-trend |
| **Total** | | | | | |
| N | 757 | 668 | 609 | 561 | |
| No. of deaths | 18 | 2 | 1 | 2 | |
| Person-years | 4776.00 | 4492.08 | 4063.50 | 3713.33 | |
| Unadjusted HR | 1.00 | 0.03 (0.01-0.17) | 0.02 (0.00-0.23) | 0.17 (0.03-0.86) | p=0.03 |
| Adjusted HR[a] | 1.00 | 0.04 (0.01-0.20) | 0.04 (0.01-0.35) | 0.30 (0.05-1.63) | p=0.07 |
| **Non-Hispanic White** | | | | | |
| N | 532 | 476 | 444 | 440 | |
| No. of deaths | 12 | 0 | 0 | 2 | |
| Person-years | 3356.50 | 3215.17 | 2962.58 | 2897.42 | |
| Unadjusted HR | 1.00 | 0.00 (0.00-0.00) | 0.00 (0.00-0.00) | 0.20 (0.03-1.06) | p=0.08 |
| Adjusted HR[a] | 1.00 | 0.00 (0.00-0.00) | 0.00 (0.00-0.00) | 0.37 (0.07-2.84) | p=0.12 |
| **Non-Hispanic Black** | | | | | |
| N | 225 | 192 | 165 | 121 | |
| No. of deaths | 6 | 2 | 1 | 0 | |
| Person-years | 1419.50 | 1276.92 | 1100.92 | 815.92 | |
| Unadjusted HR | 1.00 | 0.25 (0.06-1.04) | 0.18 (0.02-1.78) | 0.00 (0.00-0.00) | p=0.02 |
| Adjusted HR[a] | 1.00 | 0.18 (0.01-2.73) | 0.29 (0.03-2.59) | 0.00 (0.00-0.00) | p=0.13 |

[a]Adjusted for: age, gender, education, body mass index, glycemic status, healthy eating index, smoking status, alcohol consumption. HR: Hazard Ratio. Q: Quartile

**Appendix 13**

**3A. Is there a dose-response relationship between accelerometer-derived minutes of MVPA (2020) and diabetes-related mortality across race-ethnic groups?**

Using the NHANES accelerometer cutpoint of 2020 cpm (1) the dose-response relationship between accelerometer-derived minutes of MVPA2020 and diabetes-related mortality was examined. MVPA was examined continuously in 10-minute increments. Tables A13.1, A13.2 and A13.3 display the results of these analyses. Across all analyses, no significant reductions in risk were found for every 10 minute accrued of MVPA2020. Due to the lack of deaths related to diabetes as well as the low number of mean minutes of MVPA, the confidence intervals were large. Thus, no relationships were found.

1. National Health and Nutrition Examination Survey (NHANES) 2003-2004 documentation, codebook, and frequencies, MEC exam component: physical activity monitor examination data. Atlanta, GA: Centers for Disease Control and Prevention; 2007.

Table A13.1. Relationship between accelerometer-derived MVPA (2020) and diabetes-related mortality: 2003-2006 NHANES (N=2,557)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Unadjusted | Age and race-ethnicity adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *MVPA 2020 (Every 10 minutes)* | 0.33 (0.08-1.30) | 0.48 (0.12-1.97) | 0.65 (0.24-1.78) |
| **Demographics** | | | |
| *Age (years)* | | 1.06 (0.98-1.15) | 1.04 (0.97-1.11) |
| *Race-ethnicity* | | | |
| NHW | | 1.00 | 1.00 |
| NHB | | 1.76 (0.49-6.33) | 0.68 (0.17-2.65) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.52 (0.20-1.33) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 0.31 (0.07-1.01) |
| Some college | | | 0.45 (0.08-2.59) |
| College graduate | | | 0.09 (0.01-1.10) |
| **Metabolic Markers** | | | |
| *Body Mass Index* | | | 0.93 (0.86-1.00)* |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.23 (0.08-0.71)* |
| Euglycemic (A1c < 5.7%) | | | 0.01 (0.00-0.05)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index* | | | 0.97 (0.93-1.02) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.57 (0.19-1.67) |
| Non-smoker | | | 1.07 (0.40-2.85) |
| *Alcohol consumption* | | | |
| Non-drinker | | | 1.00 |
| Moderate | | | 0.38 (0.10-1.52) |
| Above moderate | | | 0.64 (0.05-7.71) |

NHW: non-Hispanic white; NHB: non-Hispanic black.
MVPA 2020: Moderate-to-vigorous physical activity (≥2020 counts/min).
Alcohol consumption: Non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).
*p<0.05

Table A13.2. Relationship between accelerometer-derived MVPA (2020) and diabetes-related mortality stratified by race-ethnicity: 2003-2006 NHANES (N=2,595)

| Variables | Hazard Ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Race-Ethnicity | | | |
| | NHW | | NHB | |
| | Unadjusted | Fully-adjusted | Unadjusted | Fully-adjusted |
| **Physical Activity** | | | | |
| *MVPA 2020 (Every 10 minutes)* | 0.37 (0.09-1.49) | 0.77 (0.30-1.99) | 0.09 (0.00-1.95) | 0.43 (0.11-1.65) |
| **Demographics** | | | | |
| *Age(years)* | | 1.04 (0.97-1.11) | | 1.10 (1.02-1.19)* |
| *Gender* | | | | |
| Male | | 1.00 | | 1.00 |
| Female | | 0.38 (0.14-1.06) | | 2.79 (0.66-11.82) |
| *Education* | | | | |
| Less than high school | | 1.00 | | 1.00 |
| High school graduate | | 0.20 (0.04-0.87)* | | 1.69 (0.34-8.47) |
| Some college | | 0.35 (0.05-2.70) | | 0.51 (0.06-4.51) |
| College graduate | | No deaths | | 5.51 (0.14-220.81) |
| **Metabolic Markers** | | | | |
| *Body Mass Index* | | 0.92 (0.83-1.02) | | 0.87 (0.83-0.92)* |
| *Glycemic Status* | | | | |
| Diabetes (A1c ≥ 6.5%) | | 1.00 | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | 0.24 (0.06-0.97)* | | 0.24 (0.09-0.64)* |
| Euglycemic (A1c < 5.7%) | | No deaths | | 0.03 (0.00-1.65) |
| **Health Behaviors** | | | | |
| *Healthy Eating Index* | | 0.96 (0.91-1.02) | | 1.01 (0.97-1.05) |
| *Smoking Status* | | | | |
| Current smoker | | 1.00 | | 1.00 |
| Former | | 0.75 (0.13-4.22) | | 0.72 (0.17-2.98) |
| Non-smoker | | 2.08 (0.63-6.90) | | 0.03 (0.00-1.65) |
| *Alcohol consumption* | | | | |
| Non-drinker | | 1.00 | | 1.00 |
| Moderate | | 0.35 (0.07-1.65) | | 0.57 (0.07-4.50) |
| Above moderate | | No deaths | | 2.78 (0.51-15.27) |

NHW: non-Hispanic white; NHB: non-Hispanic black.
MVPA 2020: Moderate-to-vigorous physical activity (≥2020 counts/min).
Alcohol consumption: Non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).
*p<0.05

## Appendix 14

## 3A. Is there a dose-response relationship between accelerometer-derived minutes of MVPA (760) and diabetes-related mortality across race-ethnic groups?

Using the Matthews et al. (1) cutpoint of 760 counts per minute (cpm) the dose-response relationship between accelerometer-derived minutes of MVPA760 and diabetes-related mortality was examined. MVPA was examined continuously in 10-minute increments. Tables A14.1, A14.2 and A14.3 display the results of these analyses. As displayed in table A14.1, in the analysis adjusting for age and race-ethnicity, a significant reduction in risk was found for every 10-minutes of MVPA760 accrued. Following adjustment for covariates, results were attenuated and significance was lost.

In unadjusted analyses stratifying by race-ethnicity, both NHW (HR 0.70, 95% CI 0.55-0.90) and NHB (HR 0.67, 95% CI 0.46-0.96) had significant reductions in risk. Following adjustment for covariates, significance was lost for NHW (HR 0.78, 95% CI 0.57-1.07) and NHB (HR 0.77, 95% CI 0.50-1.17).

The results of the analysis are promising in that the reduction in risk associated with every 10-minyes accrued of MVPA760 was 22% in NHW and 27% in NHB. However, the results were not statistically significant. As discussed in the previous appendices using the continuous NHANES, as more data are available within the NDI, the ability to examine more robust measures of PA (i.e. accelerometer-derived MVPA) and their relationship with diabetes-related mortality will become plausible.

1. Matthews CE. Calibration of accelerometer output for adults. *Med Sci Sports Exerc*. 2005;37(11 Suppl):S512-22.

Table A14.1. Relationship between accelerometer-derived MVPA (760) and diabetes-related mortality: 2003-2006 NHANES (N=2,595)

| Variables | Hazard Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Unadjusted | Age and race-ethnicity adjusted | Fully-adjusted |
| **Physical Activity** | | | |
| *MVPA 760 (Every 10 minutes)* | 0.70 (0.56-0.87)* | 0.74 (0.55-0.99)* | 0.78 (0.60-1.02) |
| **Demographics** | | | |
| *Age (years)* | | 1.04 (0.96-1.12) | 1.02 (0.96-1.09) |
| *Race-ethnicity* | | | |
| NHW | | 1.00 | 1.00 |
| NHB | | 1.62 (0.46-5.81) | 0.63 (0.16-2.51) |
| *Gender* | | | |
| Male | | | 1.00 |
| Female | | | 0.38 (0.14-1.04) |
| *Education* | | | |
| Less than high school | | | 1.00 |
| High school graduate | | | 0.26 (0.07-1.01) |
| Some college | | | 0.52 (0.11-2.53) |
| College graduate | | | 0.08 (0.01-0.99)* |
| **Metabolic Markers** | | | |
| *Body Mass Index* | | | 0.91 (0.85-0.98)* |
| *Glycemic Status* | | | |
| Diabetes (A1c ≥ 6.5%) | | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | | 0.23 (0.08-0.70)* |
| Euglycemic (A1c < 5.7%) | | | 0.01 (0.00-0.05)* |
| **Health Behaviors** | | | |
| *Healthy Eating Index* | | | 0.97 (0.93-1.01) |
| *Smoking Status* | | | |
| Current smoker | | | 1.00 |
| Former | | | 0.53 (0.18-1.60) |
| Non-smoker | | | 1.31 (0.59-2.92) |
| *Alcohol consumption* | | | |
| Non-drinker | | | 1.00 |
| Moderate | | | 0.46 (0.13-1.61) |
| Above moderate | | | 0.77 (0.06-9.88) |

NHW: non-Hispanic white; NHB: non-Hispanic black.
MVPA 760: Moderate-to-vigorous physical activity (≥760 counts/min).
Alcohol consumption: Non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).
*p<0.05

Table A14.2. Relationship between accelerometer-derived MVPA (760) and diabetes-related mortality stratified by race-ethnicity: 2003-2006 NHANES (N=2,595)

| Variables | Hazard Ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Race-Ethnicity | | | |
| | NHW | | NHB | |
| | Unadjusted | Fully-adjusted | Unadjusted | Fully-adjusted |
| **Physical Activity** | | | | |
| *MVPA 760 (Every 10 minutes)* | 0.70 (0.55-0.90)* | 0.78 (0.57-1.07) | 0.67 (0.46-0.96)* | 0.77 (0.51-1.17) |
| **Demographics** | | | | |
| *Age* | | 1.02 (0.96-1.09) | | 1.07 (0.98-1.16) |
| *Gender* | | | | |
| Male | | 1.00 | | 1.00 |
| Female | | 0.27 (0.09-0.82)* | | 2.57 (0.75-8.73) |
| *Education* | | | | |
| Less than high school | | 1.00 | | 1.00 |
| High school graduate | | 0.13 (0.02-1.07) | | 1.52 (0.29-7.93) |
| Some college | | 0.46 (0.08-2.86) | | 0.45 (0.07-2.96) |
| College graduate | | No deaths | | 4.45 (0.13-152.65) |
| **Metabolic Markers** | | | | |
| *Body Mass Index* | | 0.91 (0.83-1.00)* | | 0.87 (0.82-0.92)* |
| *Glycemic Status* | | | | |
| Diabetes (A1c ≥ 6.5%) | | 1.00 | | 1.00 |
| Pre-diabetes (A1c 5.7-6.5%) | | 0.21 (0.05-0.86)* | | 0.25 (0.08-0.80)* |
| Euglycemic (A1c < 5.7%) | | No deaths | | 0.03 (0.00-1.10) |
| **Health Behaviors** | | | | |
| *Healthy Eating Index* | | 0.96 (0.90-1.02) | | 1.01 (0.97-1.05) |
| *Smoking Status* | | | | |
| Current smoker | | 1.00 | | 1.00 |
| Former | | 0.71 (0.14-3.67) | | 0.84 (0.25-2.83) |
| Non-smoker | | 2.78 (1.01-7.63) | | 0.03 (0.00-0.50)* |
| *Alcohol consumption* | | | | |
| Non-drinker | | 1.00 | | 1.00 |
| Moderate | | 0.46 (0.11-1.96) | | 0.72 (0.11-4.85) |
| Above moderate | | No deaths | | 2.43 (0.45-13.34) |

NHW: non-Hispanic white; NHB: non-Hispanic black.
MVPA 760: Moderate-to-vigorous physical activity (≥760 counts/min).
Alcohol consumption: Non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).
*p<0.05

## Appendix 15

## Mortality Tables: NHANES III, 1999-2004 NHANES, 2003-2006 NHANES

NHANES III mortality rates: all-cause, non-diabetes related, and diabetes-related

Table A15.1. Mortality rate for diabetes-related mortality by race-ethnic group: NHANES III

| RACE | N | Death events | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-standardized mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 4563 | 127 | 62.1 (0.8) | 75.1 (1.2) | 81,008.34 | 15.7 | 12.3 |
| **Non-Hispanic Black** | 3057 | 88 | 58.0 (1.0) | 69.7 (1.0) | 54,841.50 | 16.0 | 18.1 |
| **Mexican American** | 3097 | 116 | 54.6 (1.3) | 68.3 (1.3) | 58,086.08 | 19.9 | 26.6 |

Table A15.2. Mortality rate for non-diabetes related mortality* by race-ethnic group: NHANES III

| RACE | N | Death events | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-standardized mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 4563 | 1216 | 60.6 (0.7) | 73.2 (0.6) | 81,008.34 | 150.1 | 117.1 |
| **Non-Hispanic Black** | 3057 | 634 | 54.0 (0.7) | 65.8 (0.8) | 54,841.50 | 115.4 | 136.5 |
| **Mexican American** | 3097 | 433 | 51.2 (0.8) | 64.1 (0.8) | 58,086.08 | 74.5 | 96.3 |

*Mortality from heart disease, cancer, respiratory diseases, accidents, cerebrovascular disease, Alzheimer's, influenza and pneumonia, kidney disease, or residual causes

Table A15.3. Mortality rate for all-cause mortality by race-ethnic group: NHANES III

| RACE | N | Death events | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-standardized mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 4563 | 1343 | 60.8 (0.6) | 73.4 (0.6) | 81,008.34 | 165.7 | 129.5 |
| **Non-Hispanic Black** | 3057 | 722 | 54.5 (0.6) | 66.3 (0.6) | 54,841.50 | 131.5 | 154.7 |
| **Mexican American** | 3097 | 549 | 51.8 (0.8) | 64.8 (0.8) | 58,086.08 | 94.5 | 122.8 |

Table A15.4. Mortality rate for diabetes-related mortality by race-ethnic group: 1999-2004 NHANES

| RACE | N | # of deaths | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-adjusted mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 2383 | 35 | 64.5 (1.8) | 70.7 (1.8) | 21,573.84 | 16.2 | 15.4 |
| **Non-Hispanic Black** | 944 | 27 | 61.5 (1.6) | 67.6 (1.7) | 8402.92 | 32.1 | 44.5 |

Table A15.5. Mortality rate for non-diabetes related mortality by race-ethnic group: 1999-2004 NHANES

| RACE | N | # of deaths | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-adjusted mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 2383 | 358 | 65.7 (0.6) | 71.7 (0.6) | 21,573.84 | 165.9 | 156.1 |
| **Non-Hispanic Black** | 944 | 164 | 59.5 (1.2) | 64.6 (1.3) | 8402.92 | 195.2 | 232.9 |

*Mortality from heart disease, cancer, respiratory diseases, accidents, cerebrovascular disease, Alzheimer's, influenza and pneumonia, kidney disease, or residual causes

Table A15.6. Mortality rate for all-cause mortality by race-ethnic group: 1999-2004 NHANES

| RACE | N | # of deaths | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-adjusted mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 2383 | 393 | 65.6 (0.7) | 71.6 (0.7) | 21,573.84 | 182.2 | 171.5 |
| **Non-Hispanic Black** | 944 | 191 | 59.7 (0.9) | 65.0 (1.0) | 8402.92 | 227.3 | 277.5 |

Table A15.7. Mortality rate for diabetes-related mortality by race-ethnic group: 2003-2006 NHANES

| RACE | N | # of deaths | Baseline age mean | Death age mean | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-adjusted mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 1892 | 14 | 65.5 | 70.7 | 12,431.67 | 11.3 | 10.7 |
| **Non-Hispanic Black** | 703 | 9 | 67.6 | 71.3 | 4,613.25 | 19.5 | 33.4 |

Table A15.8. Mortality rate for non-diabetes related mortality by race-ethnic group: 2003-2006 NHANES

| RACE | N | # of deaths | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-adjusted mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 1892 | 150 | 65.1 (0.6) | 69.2 (0.6) | 12,431.67 | 120.7 | 115.4 |
| **Non-Hispanic Black** | 703 | 64 | 61.6 (1.3) | 65.6 (1.5) | 4,613.25 | 138.7 | 160.4 |

*Mortality from heart disease, cancer, respiratory diseases, accidents, cerebrovascular disease, Alzheimer's, influenza and pneumonia, kidney disease, or residual causes

Table A15.9. Mortality rate for all-cause mortality by race-ethnic group: 2003-2006 NHANES

| RACE | N | # of deaths | Baseline age mean (SE) | Death age mean (SE) | Total person-years | Crude mortality rate (per 10,000 person-years) | Age-adjusted mortality rate (per 10,000 person-years) |
|---|---|---|---|---|---|---|---|
| **Non-Hispanic White** | 1892 | 164 | 65.2 (0.7) | 69.2 (0.7) | 12,431.67 | 131.9 | 126.1 |
| **Non-Hispanic Black** | 703 | 73 | 62.3 (1.1) | 66.3 (1.3) | 4,613.25 | 158.2 | 193.8 |

# VITA

William “Bill” Robert Boyer II was born on February 23, 1989 in Jacksonville, Florida. He graduated from Bartram Trail High school in 2007 and then enrolled at the University of North Florida. Following his completion of his Bachelor’s of Science in Health in Exercise Science in 2012, he then remained at UNF to pursue a Master’s degree in Exercise Science and Chronic Disease. After receiving his Master’s degree in 2014, Bill enrolled at the University of Tennessee pursing a PhD in Kinesiology with a concertation in Physical Activity Epidemiology. During his time at UT he was awarded the Andy Kozar Graduate Research Scholarship, the A.W. Hobt Memorial Scholarship, as well as the American Kinesiology Association National Writing Award. He accepted a position as a tenure-track Assistant Professor at California Baptist University in Riverside, California. He is married to his wonderful wife Hannah and they have a Jack Russell named Cooper.